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| (21) International Application Number: PCT/US98/11927 (22) International Filing Date: 10 June 1998 (10.06.98) (30) Priority Data: 08/874,807 13 June 1997 (13.06.97) US 09/079,030 14 May 1998 (14.05.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 09/079,030 (CIP) Filed on 14 May 1998 (14.05.98) US 08/874,807 (CIP) Filed on 13 June 1997 (13.06.97) (71) Applicant (for all designated States except US): BAYLOR COLLEGE OF MEDICINE [US/US]; One Baylor Plaza, Houston, TX 77030 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GUEVARA, Juan, G., Jr. [US/US]; 3015 Fairhope, Houston, TX 77025 (US). HOOGEVEEN, Ron, C. [NL/US]; 7510 Brompton #610, Houston, TX 77025 (US). MOORE, J., Paul [US/US]; 12710 Folkcrest Way, Stafford, TX 77477 (US). | | (74) Agent: MCMILLIAN, Nabeela, R.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: LIPOPROTEINS AS NUCLEIC ACID VECTORS (57) Abstract <p>The present invention relates to materials and methods for the <i>in vivo</i> transport and deliver of nucleic acids. More particularly, it concerns the use of lipoproteins, including but not limited to, low density lipoproteins ("LDL"), and/or apolipoproteins for the binding and <i>in vivo</i> transport of nucleic acids. In addition, the present invention relates to the use of lipoproteins in the early detection of cancer and/or metastatic cancer and/or arteriosclerosis.</p> | | |

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DESCRIPTION

LIPOPROTEINS AS NUCLEIC ACID VECTORS

BACKGROUND OF THE INVENTION

The present application is a continuation-in-part of co-pending U.S. Patent Application
5 Serial No. 08/874,807 Entitled "Lipoproteins As Nucleic Acid Vectors" filed June 13, 1997.
The entire text of the above-referenced disclosure is specifically incorporated by reference
herein without disclaimer.

1. Field of the Invention

The present invention relates to materials and methods for the *in vivo* transport and
delivery of nucleic acids. More particularly, it concerns the use of lipoproteins, including but
not limited to, low density lipoproteins ("LDL"), and/or apolipoproteins for the *in vivo* transport
of nucleic acids. In addition, the present invention relates to the use of lipoproteins in the early
detection of cancer and/or metastatic cancer and/or arteriosclerosis.

2. Description of Related Art

The ultimate curative method for any genetic disorder, whether the disorder is inherited
or results from a mutation, depends on an effective mode of replacing or augmenting non-
functional gene(s). This process is now termed gene or genetic therapy. There are two
20 important aspects to genetic therapy, the gene delivery system/vehicle and the gene
control/expression program. Ideally, a replacement gene should become resident in the genome
of the target cells/organism and be transferable to subsequent generations of cells and progeny,
i.e., the change is incorporated into the germ cells or reproductive cells, the sperm and ovary.
Although there have been several significant breakthroughs in this field, this area of
25 biotechnology is still in its early development phase. The first step in any approach to gene
replacement is the delivery of the specific gene (nucleic acid) to the cells.

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Many techniques have been and are being developed to deliver and express genes in cells and specific tissues in mammals *in vivo*. Several general, non-specific methods for delivering genes have been reported involving aerosol nucleic acid delivery to cells (Stribling *et al.*, 1992); calcium phosphate precipitation, using a steep change in ionic strength (Wigler *et al.*, 1979); DEAE-dextran (Sompayrac *et al.*, 1981); electroporation, forcing the nucleic acid into the cell by using an electric field or current (Neumann *et al.*, 1982); microinjection, physically injecting the nucleic acid into a cell (Benvensty *et al.*, 1986; Wolff *et al.*, 1990); and polycationic molecules such as polylysine polypeptides (Curiel *et al.*, 1992) and cationic lipids (Lee *et al.*, 1996).

Liposomes, vesicles composed of synthetic or non-natural lipids such as long-chain fatty acids, can be used to carry the nucleic acid into the cell cytoplasm non-specifically (Felgner *et al.*, 1987). A recent invention describes the delivery of a self-initiating and self-sustaining gene expression system which contains an RNA polymerase prebound to a DNA molecule using the aforementioned nucleotide delivery systems (U.S. Patent No. 5,591,601).

Viral vectors in which specific nucleic acid sequences are incorporated into a neutralized or inactivated virus can use their viral entry mechanism to gain entry to the cell cytoplasm *via* specific cellular receptors to deliver nucleic acids (Schimotohono *et al.*, 1981). The use of specific cellular receptors is apparently a more specific method for delivering genes. In this approach, the nucleic acid is bound either freely, through charge association, or alternatively it is chemically and non-reversibly conjugated to proteins with specific receptor proteins on the membrane of target cells for receptor-mediated uptake (Wu *et al.*, 1988, Wu *et al.*, 1989).

Techniques such as calcium phosphate precipitation, electroporation or DEAE-dextran transfection are not suitable for *in vivo* applications. Bombarding cells with nucleic acids under high pressure is a technique which has very limited applications in that it can only be applied topically and only a small number of cells can be targeted. Microinjection of nucleic acids into cells is mainly performed *in vitro* and requires actively dividing cells.

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Gene delivery systems that use the viral entry mechanism of recombinant viral vectors have major disadvantages. Systems that utilize replication-defective adenoviral vectors can infect a wide variety of eukaryotic cell types including quiescent somatic cells utilizing the viral entry mechanism. However, adenoviral vector-based delivery systems are only successful in transient gene expression and repeated administration of the viral vector results in a strong immunological response of the host. In addition, the host will experience an adenoviral infection and can experience its symptoms if the recombinant vector undergoes homologous recombination with the wild-type virus strain. Systems that employ recombinant retroviral vectors can be used for stable integration of the gene of interest into the host's genome, but only actively dividing cells can be targeted. In addition, the disadvantages of the adenoviral vector systems also apply to retroviral vector systems (immune response, disease *etc.*).

Positively-charged polycationic molecules such as polylysine peptides which bind non-specifically to the negatively charged nucleic acids have been used to introduce DNA into the chromosome of the recipient cell or organism. Cationic lipid vesicles, liposomes and micelles have been used in aggregates with DNA and viral envelope glycoproteins in non-specific delivery of genes. Liposomes, vesicles composed of synthetic or non-natural lipids, such as long-chain fatty acids, can be used to carry the nucleic acid into the cell cytoplasm non-specifically. In these systems, the liposomes are structured to "best fit" the nucleic acid and insertion into the cell is through non-specific uptake.

The interaction of the liposomal delivery systems discussed above with the nucleic acid to be delivered is non-specific. In addition, prior art techniques are designed to deliver multiple copies of the nucleic acid to the cell cytoplasm. Optimally, however, only one or two copies of a gene should be transfected per cell throughout the organism to replace a defective set of genes only in the specific cells and tissues where it would normally be expressed.

Thus there is a need for a safe and efficient gene delivery system that may be employed in the burgeoning field of gene therapy.

SUMMARY OF THE PRESENT INVENTION

The present invention contemplates a gene delivery system for use in gene therapy. Thus in particular embodiments, the present invention provides a composition comprising an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain; and a
5 nucleic acid comprising an LDL or VLDL binding sequence, wherein the nucleic acid is bound to the polypeptide. In particularly preferred embodiments, the polypeptide comprises an LDL nucleic acid binding domain. In other embodiments, the polypeptide comprises a VLDL nucleic acid binding domain. In particular aspects of the present invention, the nucleic acid comprises an expression region operably linked to a promoter active in eukaryotic cells. In
10 more particular embodiments, the expression region encodes a polypeptide. In other preferred embodiments, the expression region comprises an antisense construct.

In those embodiments in which the expression region encodes a polypeptide, the polypeptide may be selected from the group consisting of α -globin, β -globin, γ -globin, granulocyte macrophage-colony stimulating factor (GM-CSF), tumor necrosis factor (TNF), IL-
15 2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, β -interferon, γ -interferon, cytosine deaminase, adenosine deaminase, β -glucuronidase, hypoxanthine guanine phosphoribosyl transferase, galactose-1-phosphate uridyltransferase, glucocerebrosidase, glucose-6-phosphatase, thymidine kinase, lysosomal glucosidase, growth
20 hormone, nerve growth factor, insulin, adrenocorticotrophic hormone, parathormone, follicle-stimulating hormone, luteinizing hormone, epidermal growth factor, thyroid stimulating hormone of CFTR, EGFR, VEGFR, IL-2 receptor, estrogen receptor, Bax, Bak, Bcl-X_s, Bik, Bid, Bad, Harakiri, Ad E1B, an ICE-CED3 protease neomycin resistance, luciferase, adenine phosphoribosyl transferase (APRT), retinoblastoma, insulin, mast cell growth factor, p53, p16,
25 p21, MMAC1, p73, zac1 and BRCA1.

In those embodiments in which the expression region comprises an antisense construct, the antisense construct may be complementary to a segment of an oncogene. In more preferred
30 embodiments, the oncogene may be selected from the group consisting of *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl* and *abl*.

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The expression region may be linked to a promoter selected from the group consisting of CMV IE, LTR, SV40 IE, HSV *tk*, β -actin, human globin α , human globin β and human globin γ promoter. In a defined embodiment, the nucleic acid binding domain is an apoB100 nucleic acid binding domain. In other embodiments, the composition of the present invention may further comprise one or more lipoproteins selected from the group consisting of apoA1, apoA-II, apoA-IV, acat, apoE, apoC-II, apoC-III and apo-D. In particularly preferred embodiment, the apoB100 is selected from the group consisting of human, rat and baboon apoB100.

In particular aspects of the invention, the polypeptide comprises at least two nucleic acid binding domains. In particularly preferred embodiments, the nucleic acid binding domain contains a motif selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 γ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motif and a nucleotide (ATP)-binding motif. In more defined embodiments, the binding domain may be selected from the group consisting of SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166 and SEQ ID NO:175.

In other embodiments, the polypeptide may further comprise at least one nuclear localization sequence. More particularly, the nuclear localization sequence may be from apoB100. In more preferred embodiments, the nuclear localization sequence may be selected from the group consisting of SEQ ID NO:178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID

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NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210.

Also contemplated by the present invention is a method for expressing a polypeptide in a human cell comprising the steps of providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) a nucleic acid comprising an expression cassette comprising a sequence encoding the polypeptide and a promoter active in eukaryotic cells, wherein the coding sequence is operably linked to the promoter, and wherein the nucleic acid sequence is bound to the LDL or VLDL; contacting the composition with the cell under conditions permitting transfer of the composition into the cell; and culturing the cell under conditions permitting the expression of the polypeptide.

In particularly preferred embodiments, the polypeptide independently, is a tumor suppressor, a cytokine, an enzyme, a hormone, a receptor, or an inducer of apoptosis. In preferred embodiments, the tumor suppressor may be selected from the group consisting of p53, p16, p21, MMAC1, p73, zac1, BRCA1 and Rb. In preferred embodiments, the cytokine may be selected from the group consisting of IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, TNF, GM-CSF, β -interferon and γ -interferon. In other preferred embodiments, the enzyme may be selected from the group consisting of cytosine deaminase, adenosine deaminase, β -glucuronidase, hypoxanthine guanine phosphoribosyl transferase, galactose-1-phosphate uridylyltransferase, glucocerebrosidase, glucose-6-phosphatase, thymidine kinase and lysosomal glucosidase. In still further preferred embodiments, the hormone may be selected from the group consisting of growth hormone, nerve growth factor, insulin, adrenocorticotrophic hormone, parathormone, follicle-stimulating hormone, luteinizing hormone, epidermal growth factor and thyroid stimulating hormone. In defined embodiments, the receptor may be selected from the group consisting of CFTR, EGFR, VEGFR, IL-2 receptor and the estrogen receptor. In other preferred embodiments, the inducer of apoptosis may be selected from the group consisting of Bax, Bak, Bcl-X_s, Bik, Bid, Bad, Harakiri, Ad E1B and an ICE-CED3 protease.

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In particularly preferred embodiments, the nucleic acid binding domain is an apoB100 nucleic acid binding domain. In more preferred embodiments, the apoB100 may be selected from the group consisting of human, rat and baboon low density apoB100. In still further preferred embodiments, the binding region is selected from the group consisting of a proline
5 pipe helix DNA binding motif, a ISGF3 γ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motifs, and a nucleotide (ATP)-binding motif. In particular embodiments, the polypeptide further may comprise at least one nuclear localization sequence. In especially preferred embodiments, the nuclear localization sequence is derived from an apoB100 nuclear localization sequence. In specific embodiments, the polypeptide may be selected from the
10 group consisting of α -globin, β -globin, γ -globin, neomycin resistance, luciferase, adenine phosphoribosyl transferase (APRT), and mast cell growth factor.

Also provided is a method for providing an expression construct to a human cell comprising providing a composition comprising (i) an isolated polypeptide comprising at least
15 one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein the expression region is operably linked to the promoter, and wherein the nucleic acid sequence is bound to the LDL or VLDL; contacting the composition with the cell under conditions permitting transfer of the composition into the cell; and culturing the cell under
20 conditions permitting the expression of the expression region.

In particularly preferred embodiments, the expression construct comprises an antisense construct. In more preferred embodiments, the antisense construct is derived from an oncogene. In exemplary embodiments, the oncogene may be selected from the group consisting *ras*, *myc*,
25 *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl* and *abl*. In other embodiments, the expression construct comprises a nucleic acid coding for a gene. In preferred aspects the gene encodes a polypeptide.

In particularly preferred embodiments, the nucleic acid binding domain is an apoB100
30 nucleic acid binding domain. The apoB100 may be selected from the group consisting of human, rat and baboon low density apoB100. In other preferred embodiments, the DNA

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binding region is selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 γ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motifs, and a nucleotide (ATP)-binding motif.

5 Further the present invention contemplates a method for treating a human disease comprising providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein the expression region is operably linked to the promoter, and wherein the nucleic acid
10 sequence is bound to the LDL or VLDL; and administering the composition to a human subject having the disease under conditions permitting transfer of the composition into cells of the human subject.

In specific embodiments, the disease may be selected from the group consisting of
15 cancer, diabetes, cystic fibrosis and arteriosclerosis. In preferred embodiments the polypeptide comprises at least two nucleic acid binding regions. In other preferred embodiments the polypeptide comprises at least one nuclear localization sequence. In particularly preferred embodiments, the nucleic acid encodes a gene. In other preferred embodiments, the expression construct comprises an antisense construct.

20 Another aspects of the present invention describes a pharmaceutical composition comprising an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain; and a nucleic acid comprising an LDL or VLDL binding sequence, wherein the nucleic acid is bound to the polypeptide; the pharmaceutical composition being dispersed in a suitable
25 diluent.

Also contemplated by the present invention is a method of transforming a cell comprising providing a cell; contacting the cell with a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an
30 expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein the expression region is operably linked to the

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promoter, and wherein the nucleic acid sequence is bound to the LDL or VLDL; wherein expression of the expression region is indicative of the transformation.

Yet another aspect of the present invention contemplates a method of transfecting a cell comprising the steps of providing a cell; contacting the cell with a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein the expression region is operably linked to the promoter, and wherein the nucleic acid sequence is bound to the LDL or VLDL; wherein expression of the expression region is indicative of the transfection.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG. 1A-FIG. 1C show the amino acid sequence of apoB-100.

FIG. 2A-FIG. 2F is a homology alignment of SH3-like regions in apo B-100 with known SH3 domains of signal transduction proteins. FIG. 2A-FIG. 2D are the homology alignments and FIG. 2E and FIG. 2F identify the regions of apo B-100 and the proteins aligned.

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FIG. 3A-FIG. 3D show a comparison of SH2-like regions in apo B-100 to known SH3 domains of signal transduction proteins. FIG. 3A-FIG. 3C are the homology alignments, FIG. 3D identifies the proteins and regions aligned.

5 FIG. 4A-FIG. 4C show a comparison of the apo B-100 SH 1-like region to SH1 kinase domains of known signal transduction proteins. FIG. 4A and FIG. 4B shows the alignments; FIG. 4C identifies the proteins and regions aligned.

10 FIG. 5A and FIG. 5B show the inter-kringle proline-rich regions of Apo[a] compared with the proline rich region of SH3-binding protein (3BP1). FIG. 5A shows the alignment; FIG. 5B identifies the proteins and regions aligned.

15 FIG. 6A and FIG. 6B show an homology alignment of specific regions of apo B-100 and the activation regions located at the amino- and carboxyl- termini of signal transduction proteins.

FIG. 7 illustrates the homology of specific regions of apo B-100 with proline pipe helix motifs of Tus.

20 FIG. 8A-FIG. 8D show a homology alignment among one region of the DNA-binding protein ISGF3 γ and similar regions in apo B-100.

FIG. 9A-FIG. 9D show a homology alignment among regions of the DNA-binding protein ISGF3 γ and similar regions in apo B-100.

25 FIG. 10A-FIG. 10N. FIG. 10N shows a sequence comparison of the DNA-binding domains of the SREBP1, SREBP2, and ADD1 proteins with similar regions found in apo B-100. FIG. 10B-FIG. 10N show a sequence comparison of the DNA-binding domains of SREBP1 with various apolipoproteins.

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FIG. 11 shows a comparison of the primary structures of known coiled-coil regions of DNA-binding proteins and analogous regions in apo B-100.

FIG. 12A-FIG. 12C show a comparison of known ATP-binding loop motifs to similar regions in apo B-100.

FIG. 13A-FIG. 13E show a comparison of known nuclear localization signal sequences to similar regions in apo B-100.

FIG. 14A-FIG. 14J show a comparison of human apo B-100 regions with sequenced regions of apo B-100 from other species.

FIG. 15 shows the composition of the LDL gene delivery system of the instant invention. LDL containing apo B-100 is depicted along with a DNA sequence containing a promoter, a protein coding region, a 3' untranslated region, and a non-coding region.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention arises from the discovery that regions of apolipoproteins, the protein fraction of lipoprotein particles, are similar in primary structure and amino acid sequence to cellular proteins which are known to bind to DNA. Presently, the only known functions of lipoproteins VLDL, IDL, LDL and HDL are the solubilization and transport of hydrophobic lipids in plasma. The instant invention shows that LDLs, but not other lipoproteins, form a complex with DNA.

Herein, synthetic analogues of regions of DNA have been shown to bind to highly purified preparations of human, rat, and baboon LDL but not to other human lipoproteins such as VLDL and HDL, nor to mouse lipoproteins. In fact, the differences observed among the four species tested suggests that human, rat, and baboon lipoproteins behave very similarly in terms of DNA binding preference. Further, purified preparations of human, rat, and baboon LDLs are shown to complex with the promoter region of the human cytomegalovirus. Thus, the present invention demonstrates that human LDL complexes with specific regions of genomic DNA.

Because lipoproteins have specific cell membrane receptors and are actively and specifically internalized by many different cell types in mammals, and because the inventors show that LDL can bind DNA, these lipoproteins can be used as gene delivery vectors. More specifically, this invention relates to materials and methods for the use of lipoproteins, such as LDL, or, for example, apolipoproteins such as, but not limited to, apoB-100, apoA1, apoE, apoAIV, and apoC, or more specifically still, the DNA binding regions of these lipoproteins, as gene delivery vectors *in vivo*. As explained in greater detail below, the various embodiments of this invention include, but are not limited to, the delivery of nucleic acids to a cell in the form of an LDL-lipoprotein complex, the specific delivery of DNA to the nucleus, and the specific localization of delivered DNA to specific nuclear sites.

Plasma levels of DNA increase in a variety of chronic diseases including lupus erythematosus (Steinman, 1984), viral hepatitis (Neurath *et al.*, 1984), and a variety of cancers (Leon *et al.*, 1977; Shapiro *et al.*, 1983; Stroun *et al.*, 1987; Nawroz *et al.*, 1996; Anker *et al.*, 1997; Chen *et al.*, 1996). It further has been shown that lipoproteins in the blood of non-tumor carrying organisms are not bound to nucleic acids. However, cancer-carrying individuals, and in particular individuals with metastatic cancers, release large amounts of nucleic acids, into the blood. Thus, this invention also relates to the observation that lipoproteins in the blood of cancer patients and especially metastatic cancer patients are bound to nucleic acids, including DNA. Accordingly, this invention also may be used to provide a simple screening test for the presence or absence of cancer, especially metastatic cancer, by isolating a patient's lipoproteins and determining whether the lipoproteins are bound to nucleic acids; the presence of lipoprotein-bound nucleic acid being correlative with the presence of cancer and/or metastatic cancer in the living body. Further embodiments of the present invention relate to the sequence specific detection of DNA bound to lipoproteins in a cancer patient as a method for the identification of specific types of cancer in a living body. These and other aspects of the present invention are discussed in greater detail below.

1. LIPOPROTEINS

Lipoproteins appear as micro-pseudomicellar particles in the blood plasma of all mammalian species including humans. Their major function is to transport lipids and other hydrophobic compounds (*i.e.*, fat-soluble vitamins) through the aqueous environment of the blood stream to their specific target cells. The transported lipids can be used as a major substrate for energy metabolism (*i.e.*, triglycerides), structural components for cell membranes (*i.e.*, phospholipids and cholesterol), or as precursors for steroid hormones and bile acids (*i.e.*, cholesterol). Although, lipoproteins vary widely in size and lipid content, they have a common general structure. Lipoprotein particles are believed to be spherical and consist of a hydrophobic core containing nonpolar lipids surrounded by a hydrophilic surface monolayer of polar lipids and proteins, which are called apolipoproteins.

Plasma lipoproteins may be separated into five major classes based on their density, size, and compositional and functional properties: 1) chylomicrons, 2) very low density lipoproteins (VLDL), 3) intermediate lipoproteins (IDL), 4) low density lipoproteins (LDL), and 5) high density lipoproteins (HDL). The different classes of lipoproteins show distinct compositional differences in apolipoprotein content. The specific role of each class of lipoproteins in lipid metabolism is determined by the interaction of these apolipoproteins with specific enzymes and cellular receptors.

a. ApoB100 Structure and Function

The major protein constituent of LDL is apoB-100. ApoB-100 is one of two known natural ligands for the LDL (apoE/apoB) receptor which is found on the surface of a wide variety of mammalian cell types (Brown and Goldstein, 1986). LDLs are taken up by a process called receptor-mediated endocytosis (Brown and Goldstein, 1986). Hence, lipoproteins may be able to function as naturally-occurring liposomes which contain protein constituents that can bind specifically to nucleic acids and can be internalized by a wide variety of eukaryotic cell types *via* specific receptor mediated processes.

Human apolipoprotein B-100 (apoB-100) is a major apoprotein component of very-low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins

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(LDL), and lipoprotein[a] (Lp[a]). ApoB-100 is synthesized and incorporated into VLDL and Lp[a] by the liver. Human LDL can be described as a spherical particle composed of a hydrophobic core of cholesterol esters and triglycerides encapsulated by an amphipathic monolayer of phospholipids, glycolipids and cholesterol in which the apoB-100 is partially imbedded (Myant, 1990). In addition to one molecule of apoB-100, LDL is known to contain varying numbers of apo C-I, apo C-II, apo C-III, apo E, and apo D (Blanco-Vaca *et al.*, 1992; Connelly *et al.*, 1993; Blanco-Vaca *et al.*, 1994).

The primary structure of apoB-100, SEQ ID NO:1 (FIG. 1A-FIG. 1C) has been determined by amino acid sequence analysis (Yang *et al.*, 1986; Yang *et al.*, 1989) and inferred from its cDNA sequence (Yang *et al.*, 1986; Yang *et al.*, 1989; Knott *et al.*, 1986). There appear to be several different isoforms of apo B-100. The isoform shown in FIG. 1A-FIG. 1C is the isoform used for all of the alignments in the specification. Homologous regions in the other isoforms, however, would align similarly.

The apparent molecular weight of apoB-100 is 512 kDa based on its amino acid composition of 4536 residues. The apoprotein contains 25 Cys residues (Coleman *et al.*, 1990; Yang, 1990), at least 16 of which form intramolecular disulfide bonds, with the remaining cysteines present as free sulfhydryls, as additional (unassigned) intramolecular disulfides, or as intermolecular disulfide linkages to other apolipoproteins (Blanco-Vaca *et al.*, 1992; Connelly *et al.*, 1993). Several important functional regions on apoB-100 that have been identified include heparin-binding sites (Cardin *et al.*, 1987; Weisgraber and Rall, 1987), glycosylation sites (Knott *et al.*, 1986; Innerarity *et al.*, 1986), and the LDL receptor-binding region (Blanco-Vaca *et al.*, 1992, Knott *et al.*, 1986, Milne *et al.*, 1989).

ApoB-100, and apolipoprotein E (apoE), apolipoproteins present in the low-density lipoprotein group, function as ligands for the high-affinity receptor-mediated removal of certain lipoproteins from plasma by the liver and delivery of cholesterol and cholesterol esters to a variety of target tissues (Myant, 1990; Innerarity *et al.*, 1986; Brown and Goldstein, 1986; Mahley, 1988). A general mechanism for the receptor mediated uptake of LDL is well-

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established (Myant, 1990; Innerarity *et al.*, 1986; Brown and Goldstein, 1986; Mahley, 1988), and the role of the apoB-100 molecule in this mechanism also is well defined.

Specific binding of low density lipoproteins to their mammalian cell receptors depends
5 on the presence and conformation of the apoB-100 ligands (Kinoshita *et al.*, 1990). Several reports have shown that the interaction of apoB-100-lipoproteins with the up-regulated, high affinity LDL (apoB/apoE) receptor is modulated by the lipid composition of the particle (Teng *et al.*, 1985; Marcel *et al.*, 1988), by other apoproteins such as apo[a] in Lp[a] (Kostner and Grillhofer, 1991; Young *et al.*, 1986) and apoE in β -VLDL (Innerarity *et al.*, 1986; Mahley,
10 1988), and by monoclonal antibodies to specific regions of the apoB-100 molecule (Innerarity *et al.*, 1986; Young *et al.*, 1986).

In searching the apoB-100 sequence for regions of sequence similarity to other proteins, nucleic acid binding regions (deoxyribonucleic acids, DNA and ribonucleic acids, RNA),
15 nucleotide-binding regions, and nuclear-localization regions in the amino acid sequence of apoB-100 and apoE, have been identified. The present invention demonstrates that highly purified preparations of human, rat, and baboon LDL bind specifically to pure preparations of human genomic DNA. These properties impart to the lipoproteins the capacity to serve as delivery vehicles for genetic material.

Lipoprotein particles carry a variety of vitamins and steroid compounds in their pseudo-micelle lipid core which may function in the control of gene expression. These attributes impart to the lipoproteins a virus-like character as well as capacity. While the inventors do not wish to be bound by any particular theory, the many control elements and signal motifs in the primary
25 structure of the apolipoproteins are suggestive of the ability of these proteins to transport nucleic acids, enter the cell, participate in signal transduction, enter the nuclear space, initiate incorporation of nucleic acid materials into the resident genome, and cause its subsequent expression. As used herein, the term "primary structure" refers to the amino acid sequence of the protein. The capacity of purified LDL to bind to human genomic DNA, along with apoB-
30 100's homology to SH1, SH2, and SH3 signal transducer domains supports this hypothesis.

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These properties of apoB100, and methods of exploiting these properties, are discussed in further detail below.

2. NUCLEIC ACID BINDING REGIONS

The inventors have found that apo B-100 is also involved in DNA binding. DNA is the genetic blueprint that contains the information necessary for cell growth, differentiation, proliferation, and cellular response to environmental factors. The phenotypic differences between various cell types in higher eukaryotes are mainly due to differences in cellular gene expression.

The regulation of gene expression is predominantly controlled at the stage of initiation of transcription and is mediated by proteins which recognize specific DNA sequences. In order to recognize and bind to a specific DNA sequence a protein utilizes a structural motif. Over the past 15 years, several structural DNA binding motifs have been identified including as zinc fingers, helix-turn-helix, basic helix-loop-helix, KH RNA-binding motifs and leucine zippers and proline pipe helices. The inventors report here the identification of regions in apo B-100 with homology to various DNA binding motifs including: 1) Proline pipe helix DNA binding motifs, 2) ISGF3 γ -like DNA binding motifs, 3) SREBP-like DNA binding motifs, 4) coiled-coil motifs, and 5) nucleotide (ATP)-binding motifs.

a. Nucleotide and ATP Binding Motifs

The inventors discovered that there is a certain degree of homology between regions of apo B-100 and known ATP binding motifs found in other proteins including those involved in signal transduction and transcriptional-ribonucleotide synthesis (t-RNA synthetases. Typically, these proteins contain sites which interact with different regions of the nucleotide, *i.e.*, negatively charged phosphate regions, the ribose (carbohydrate) hydroxyl groups, and the base. A second site binds to the substrate ligand such as any amino acid in the case of t-RNA synthetases and tyrosine, serine and threonine residues in the phosphorylation of proteins.

Examination of the apoB-100 primary structure reveals several regions which are similar in sequence to the known nucleotide and ATP binding motifs and are suggestive of a similar

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function. For example, ATP-binding sites are known to contain an essential ATP-binding lysine residue. In *lyn*, the site is T₂₆₉KVAVTLKPG (SEQ ID NO:54) and in *lyk*, it is D₃₈₆KVAIKTIREG (SEQ ID NO:55). A similar region can be found in apoB-100, DLNAVANKIAD (SEQ ID NO:56). The similarity of this region in apo B-100 with the ATP-binding sites on known tyrosine-kinases suggests that apo B-100 can bind to the nucleic acid, ATP.

A single ATP-binding region occurs between residues 3800 and 3840 which is located in the kinase domain of apoB-100. The sequence of this region with known ATP-binding regions of kinases is shown in FIG. 12A-FIG. 12C. FIG. 12A-FIG. 12C show a comparison of known ATP-binding loop motifs to similar regions in apo B-100. Bold letters indicate conserved amino acids, critical amino acids (H and K) are indicated by the #, "*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the proteins, and identical amino acids between the sequences in "C" are listed below the alignment. Sequence identification numbers are listed in the right margin. The critical lysine residue is retained and the degree of similarity suggests a like function.

The ATP-binding motifs typical of t-RNA synthetases are characterized by the signature sequence HIGH (histidine, isoleucine, glycine histidine) SEQ ID NO:177, and a second motif which contains a critical lysine residue. These motifs are located within 300 residues and occur as proximal loops on the surface of the protein molecule. Several analogues of this signature sequence occur in the apoB-100 sequence (see FIG. 7 and FIG. 12A-FIG. 12C). An extended comparison of apoB-100 regions which contain the HIGH signature sequence is made with the tyrosyl-tRNA synthetase sequence shown in FIG. 12A-FIG. 12C.

b. Proline Pipe Helix Structures

The proline pipe helix is usually present in proteins that contain proline every fifth position (Myant, 1990) in the amino acid sequence that is at least 20 residues long (PXXXXP)_n (SEQ ID NO:75) where n>4. In the proline pipe helix, 5.56 residues are required to make one complete left handed helical turn. The proline pipe helix is stabilized by a hydrogen bonding network between the C=O groups of residues in positions i+ 1, i+2, i+3 (where i is a proline or

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sometimes non-proline residue) with the NH groups in positions i+2, i+3, i+4, respectively, of the following turn (Blanco-Vaca *et al.*, 1992). The unusually large turn of the helix results in the formation of a channel running along the helix that is about 6Å in average diameter (Myant, 1990) and large enough to accommodate water (Blanco-Vaca *et al.*, 1992) and possibly other molecules.

One function of the proline pipe helix is DNA binding. For example, the proline pipe helix in *Tus* is involved in tight binding to highly specific 22-23 base pair DNA known as *Ter* sites (Connelly *et al.*, 1993; Blanco-Vaca *et al.*, 1994). Because of its large diameter compared to the α -helix, the proline pipe helix spans the entire width of the major groove (Blanco-Vaca *et al.*, 1992) and results in a tight and highly specific fit. This tight fit also results in a high correspondence between the positively charged amino acid residues of the proline pipe helix and the negatively charged phosphate groups of DNA (Blanco-Vaca *et al.*, 1992). The occurrence of the proline pipe-DNA interactions in nature might be more widespread than presently thought and this interaction might play a very important biological function.

Careful examination and analysis of the apoB-100 amino acid sequence shows that the 40-residue proline-rich segment P2682-I2719, or a portion of this segment, assumes a proline pipe helical conformation (see FIG. 7), PDFRLPEIAIPEFIHPTLNLNDFQVPDLHIPEFQLPHISH (SEQ ID NO:76). Because the unique features of the proline pipe helix make it suitable for tight and highly specific DNA binding, this segment or motif in apoB-100 constitutes one of the DNA binding sites.

The functional implications of DNA binding by apoB-100 include, but are not limited to: 1) binding of DNA such as, for example, microsatellite DNA (Connelly *et al.*, 1993; Blanco-Vaca *et al.*, 1994) to apoB-100 or its fragment(s) for DNA transport from the cytoplasm to the nucleus; (2) binding of apoB-100 or its fragment(s) to the nuclear DNA to regulate transcription or effect other functions; or (3) binding of DNA to apoB-100 or its fragment(s) to transport DNA from the nucleus to the cytoplasm. Other functions as a consequence of apoB-100 DNA binding through the apoB-100 proline pipe helix are not precluded. Therefore, the

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proline pipe region of apoB-100 constitutes an important target for structure-based drug design and delivery systems.

c. ISGF3 γ -like DNA binding motifs

ISGF3 is a multimeric transcription factor involved in the regulation of transcription of a large set of genes. This factor dissociated into two protein components termed ISGF3 γ and ISGF3 α . ISGF3 γ is a 48 kDa protein that binds DNA recognizing the IFN-stimulated response element. ISGF3 α does not bind DNA. Regions in apoB-100 have been found to be homologous to the DNA-binding domain of ISGF37 (FIG. 8A-FIG. 8D and FIG. 9A-FIG. 9D).

FIG. 8A-FIG. 8D show a homology alignment among one region of the DNA-binding protein ISGF3 γ and similar regions in apo B-100. Basic amino acids are indicated in bold and * indicates conserved amino acids between the two regions and V indicates conserved amino acids that have switched positions between the two sequences aligned. Sequence identification numbers are identified in the legend to the figure.

FIG. 9A-FIG. 9D show a homology alignment among regions of the DNA-binding protein ISGF3 γ and similar regions in apo B-100. Basic amino acids are indicated in bold, "-" indicates gaps introduced in the sequence in order to align the two proteins. Sequence identification numbers are identified in the right margin.

This indicates apoB-100 can bind specific DNA sequences in a manner similar to ISGF3 γ .

d. SREBP-Like DNA Binding Motifs

Another region within apoB-100 shows striking resemblance to the DNA binding domains of previously identified sterol regulatory element binding proteins (SREBP's; FIG. 10A and FIG. 10B). A sequence comparison of the DNA-binding domains of the SREBP1, SREBP2, ADD1 proteins with similar regions found in apo B-100 are shown in FIG. 10A where basic amino acids are indicated in bold, "*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins, and identical amino

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acids between the two sequence are listed below the alignment. FIG. 10B shows a sequence comparison of the DNA-binding domains of SREBP1 with various apolipoproteins where basic amino acids are indicated in bold, "*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins. V indicates conserved amino acids that have switched positions between the two sequences aligned, and identical amino acids between the two sequences are listed below the alignment. Sequence identification numbers are indicated in the legend to the figure. The full line of "*****" separates the different sequence alignments.

SREBP's are members of the basic helix-loop-helix-leucine zipper (bH-L-H-Zip) family of transcription factors and play a major role in the transcriptional regulation of a number of genes involved in cholesterol homeostasis as well as lipid biosynthesis. SREBP's contain 3 segments: 1) an NH₂ terminal bH-L-H-Zip DNA binding domain including an acidic transcription activating domain; 2) a middle segment containing two membrane spanning domains; and 3) a COOH terminal segment. In order for SREBP's to become functionally active transcription factors, their NH₂ terminal domain containing the bH-L-H-Zip region needs to be released from the endoplasmic reticulum or nuclear envelope. This process is mediated by a sterol-regulated protease. That apo B-100, like the SREBP's, binds DNA.

e. Coiled-coil Motif (Leucine Zipper)

The coiled-coil motif (Myant, 1990), sometimes referred to as the leucine zipper (Blanco-Vaca *et al.*, 1992), is characterized by two α -helical chains that wrap around each other to form a left-handed supercoil. The amino acid sequence of coiled-coil forming proteins is characterized by the presence of heptad repeats, that is, three or more repeats of a seven-residue sequence where every third and every fourth position in the heptad is occupied by a hydrophobic residue (Blanco-Vaca *et al.*, 1992; Connelly *et al.*, 1993; Blanco-Vaca *et al.*, 1994). The two α -helical chains that form the coiled-coil can align either in parallel or anti-parallel orientation and their stabilities are dependent on the presence of strategically located hydrophobic and electrostatic interactions (Yang *et al.*, 1986; Yang *et al.*, 1989; Knott *et al.*, 1986; Coleman *et al.*, 1990; Yang, 1990; Cardin *et al.*, 1987; Weisgraber and Rall, 1987; Innerarity *et al.*, 1986; Milne *et al.*, 1989; Brown and Goldstein, 1986). The most attractive

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feature of the coiled-coil is that highly specific interactions can be tailored by redesigning this relatively simple motif.

The coiled-coil motif occurs widely in native proteins (Lupas *et al.*, 1991; Cohen and Parry, 1986). It plays structural and functional roles in fibrous proteins such as keratin, myosin, elastin, fibrinogen, tropomyosin, *etc.* The coiled-coil motif also serves as the dimerization domain for a number of transcription factors such as GCN4 (O'Shea *et al.*, 1991; Ellenberger *et al.*, 1992), GAL4 (Kraulis *et al.*, 1992; Baleja and Sykes, 1991; Marmorstein *et al.*, 1992), c-Fos-c-Jun (Glover and Harrison, 1995), where only the dimeric form binds to DNA and is active. It is found in globular proteins, such as tRNA synthetase (Cusack *et al.*, 1990; Biou *et al.*, 1994), and serves as anchors into the tRNA. Naturally occurring coiled-coils can also be found as three-stranded (Bullough *et al.*, 1994a; Bullough *et al.*, 1994b) or four-stranded (Banner *et al.*, 1987) structures.

Sequence alignment analysis of apoB-100 predicts that there are at least eight coiled-coil structures of varying lengths in different regions of its amino acid sequence (FIG. 11). FIG. 11 shows a comparison of the primary structures of known coiled-coil regions of DNA-binding proteins and analogous regions in apo B-100. Bold letters indicate conserved amino acids. Sequence identification numbers are listed in the right margin.

While the inventors do not wish to be bound by any particular theory, it is likely that these coiled-coil domains play very important structural and functional roles that, in turn, are vital to the function of LDL. For example, the coiled-coil motif can serve as dimerization or multimerization sites that may be important in LDL solubilization or aggregation. The coiled-coil motif can also bind DNA, RNA or nucleotides and, therefore, plays a very important role in the regulation and energetics of protein synthesis. The coiled-coil motif can also serve as a template for transport of molecules within and between the cytoplasm and the nucleus. In addition, the coiled-coil motif can also serve as a (temporary) reservoir of ligands that may be important in the regulation of the metabolic pathways. This list is by no means exhaustive, but demonstrates the biological importance of the coiled-coil motif in apoB-100.

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The discovery of the coiled-coil motif in apoB-100 and the important biological implications of its presence, apoB-100 by itself or as part of LDL, constitutes an important target for structure-based drug design, delivery, and diagnostic systems. Coiled-coil forming sequence in apoB-100 (as indicated in FIG. 11) can be used to design, study and manufacture coiled-coil based peptide or protein delivery systems for drugs, radioisotopes, oligonucleotides, genes, antigens, antibodies, epitopes for vaccines, sugars, carbohydrate analogs and other ligands to specific targets in cells, tissues and organs. Either single strand or multiple strands of the apoB-100 coiled-coil forming peptide sequences that can be used as components of or attached to the aforementioned ligands either by covalent or non-covalent methods.

Coiled-coil forming sequences in apoB-100 (FIG. 11), or fragments, analogs, or modifications therefore can be used as site-specific targets for the delivery of drugs, radioisotopes, oligonucleotides, genes, antigens, antibodies, epitopes for vaccines, sugars, carbohydrate analogs and other ligands. Site-specific targeting includes the use of coiled-coils, coiled-coil forming peptides, or any functional group that binds to the aforementioned coiled-coils sequences in apoB-100.

3. NUCLEAR LOCALIZATION SIGNALS

In addition to homology with DNA binding proteins, apoB-100 contains several regions that are homologous to known nuclear localization signals (FIG. 13A-FIG. 13E). These signals include the NLS from human p53, Abl, and apoJ. FIG. 13A-FIG. 13E show a comparison of known nuclear localization signal sequences to similar regions in apo B-100.

The bipartite nuclear localization signal contains two essential elements comprised of basic amino acids, H (histidine), R (Arginine), and K (Lysine) which are required for nuclear targeting. The signal motifs starts with two basic amino acids which are then followed by a ten to thirty amino acid spacer and a basic duster of five amino acids three of which must be basic. Approximately 50% of the known nuclear proteins listed in the protein databases have this motif, while less than 5% of non-nuclear proteins have it. FIG. 13A and FIG. 13B show sequences in apoB-100 with the perfect 10 amino acid spacer between the bipartite nuclear localization sequence element.

There is no strict requirement for the spacer length other than perhaps flexibility in the amino acids, *i.e.*, the dihedral angles. Indeed, there are basic amino acid clusters in the apo B-100 molecule that are separated by longer spacers and are nevertheless potential DNA-binding regions. FIG. 13C shows sequences in apoB-100 with more or less than 10 amino acids in the spacer region between the bipartite nuclear localization sequence element, and FIG. 13D-FIG. 13E show sequences in apoB-100 with more or less than 10 amino acids in the spacer region between an imperfect "bipartite" nuclear localization sequence element.

Thus, these regions in apoB-100 are NLS sequences capable of directing DNA to the nucleus of a cell. Apolipoproteins present on human LDL can bind to DNA through the DNA binding motifs identified herein. The functional bH-L-H-Zip domain within apoB-100 can enter the nucleus, following proteolytic release and/or aided by the nuclear localization signal domains present within the apolipoproteins, and regulate transcription of the target genes.

In addition, apo B-100 appears to be conserved across species. FIG. 14A-FIG. 14J show various regions of human apo B-100 aligned with the sequenced fragments of the apo B-100 from pig, rat, hamster, mouse, chicken and rabbit. Bold and underlined letters indicate positively charged, basic amino acids, and "-" indicates gaps introduced in the sequence in order to align the proteins:

4. HOMOLOGY TO SIGNAL TRANSDUCING PROTEINS

The inventors have found that in addition to homology with nuclear localization signals and DNA binding proteins, apoB-100 molecule has regions of sequence similarity to known motifs in a variety of signal transduction molecules. For example, regions of apo B-100 are homologous to src homology 3 (SH3) (FIG. 2A-FIG. 2F), src homology 2 (SH2) (FIG. 3A-FIG. 3D) and src homology 1 (SH1) (FIG. 4A-FIG. C) kinase domains that are common to protein tyrosine kinases of the signal transduction system (Koch *et al.*, 1991; Pawson, 1992; Schlessinger, 1994; Margolis, 1992; Waksman *et al.*, 1993; Carpenter, 1992; Ugi *et al.*, 1994; Lowenstein *et al.*, 1992; Guevara, Jr. *et al.*, 1994), as well as activation regions located at the amino-and carboxyl- termini of signal transduction proteins (FIG. 6A and FIG. 6B).

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FIG. 2A-FIG. 2F is a homology alignment of SH3-like regions in apo B-100 with known SH3 domains of signal transduction proteins, where "*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins, identical amino acids between the two sequences are listed below the alignment, and percent similarity is indicated in the right margin. This alignment is followed by a table identifying the regions of apoB-100 and the various proteins aligned to these regions along with their respective sequence identification numbers.

FIG. 3A-FIG. 3D show a comparison of SH2-like regions in apo B-100 to known SH3 domains of signal transduction proteins, where structurally important motifs are indicated by double underline, basic amino acids are indicated in bold, "*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins, identical amino acids between the two sequences are listed below the alignment, and percent similarity is indicated in the right margin. The alignment is followed by a table identifying the reference proteins and regions of apoB-100 in the alignment along with their sequence identification numbers.

FIG. 4 shows a comparison of the apo B-100 SH1-like region to SH1 kinase domains of known signal transduction proteins where basic amino acids are indicated in bold, "*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins, and identical amino acids between the two sequences are listed above the alignment. The alignment is followed by a table identifying the reference proteins and the region of apoB-100 used for the alignment along with their respective sequence identification numbers.

FIG. 6A and FIG. B show a homolog alignment of specific regions of apo B-100 and the activation regions located at the amino- and carboxyl- termini of signal transduction proteins where "*" indicates conserved amino acids, "-" indicates gaps introduced in the sequence in order to align the two proteins, and identical amino acids between the two sequences are listed above the alignment. Numbers in parenthesis indicate amino acid residues shown in the alignment and sequence identification numbers are listed in the right margin.

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Discovery of these motifs in the apoB-100 sequences was based on a series of reports (Ye *et al.*, 1988; Trieu and McConathy, 1990; Trieu *et al.*, 1991) which showed that free proline inhibited binding of recombinant apo[a] to both Lp[a] and LDL. These results implied that proline within the apoB-100 sequence interacted with the kringle binding pocket. Molecular modeling was used to determine if proline is a ligand for the different apo[a] kringle types (Guevara, Jr. *et al.*, 1993). These studies concluded that although free proline can be accommodated by the ligand binding site of several apo[a] kringle types, proline located within a polypeptide chain probably does not fit into any of the ligand binding sites of apo[a] kringles. As an alternative possibility, proline might bind at an allosteric site on the kringle structure (Guevara, Jr. *et al.*, 1993), and thereby alter the ligand binding site of the kringle. A second possibility is that apo[a] kringles are not involved at all, but rather that the proline/threonine-rich inter-kringle regions (IKR's) associate with specific sites on apoB-100, and thereby enable recombinant apo[a] to bind to Lp[a] and LDL.

a. The SH3 Domain

The interkringle regions of Apo [a] have homology to 3BP1 (FIG. 5). FIG. 5 shows the inter-kringle proline-rich regions of Apo[a] compared with the proline rich region of SH3-binding protein (3BP1) where the conserved prolines are indicated in bold and "-" indicates gaps introduced in the sequences in order to align the two proteins. Following the alignments is a table identifying the inter-kringle proline-rich regions of Apo[a] and the proline-rich region of 3BP1 used for the alignment along with their respective sequence identification numbers.

Apo[a] is a hydrophilic, glycosylated apoprotein that is disulfide-linked to apo B-100 in the Lipoprotein[a] particle. The proline-rich hinge between kringle structures of the apo[a] are suggestive a of role in signaling. Cicchetti *et al.* (1992) and Ren *et al.* (1993) described a ten amino acid, proline-rich segment of the 3BP-1 protein which binds to an SH3 domain in Abl, a non-receptor protein tyrosine kinase involved in signal transduction. The proline-rich IKR's in apo[a] (McLean *et al.*, 1987; Guevara, Jr. *et al.*, 1992), like those in 3BP-1, contain the sequence PXP (SEQ ID NO:2) which is important for the interaction of these motifs with their corresponding SH3 domains.

Proline-rich binding proteins (BP's), SH3, and SH2 domains are regulatory domains in signaling proteins which mediate enzymatic activity, participate in intracellular protein-protein interactions, and bind to activated receptor protein-tyrosine kinases (Koch *et al.*, 1991; Pawson, 1992; Schlessinger, 1994; Margolis, 1992; Waksman *et al.*, 1993; Carpenter, 1992; Ugi *et al.*, 1994; Lowenstein *et al.*, 1992; Guevara, Jr. *et al.*, 1994; Pleiman *et al.*, 1994). The sequence similarities noted between apo[a] IKR's and the proline-rich segment of 3BP-1 suggest a similar function for these regions of the apo[d] in non-covalent interactions between apo[a] and apoB-100, *i.e.*, binding of a proline-rich region in apo[a] to an SHB-like region in apoB-100.

In apoB-100, at least 13 regions share high sequence similarities with SH3 domains. SH3 domains are found in several signal transduction proteins such as phosphatidylinositol-3' kinase (PI3K) and the non-receptor tyrosine kinase Abl (see FIG. 1 and FIG. 4). This suggests that apo B-100 may have signal transduction properties.

b. The SH2 Domain

Many signal transduction proteins and other proteins such as tyrosine phosphatases and tensin also contain SH2 domains (Koch *et al.*, 1991; Pawson, 1992; Schlessinger, 1994; Lowenstein *et al.*, 1992), often flanked by SH3 domains. SH2 domains are typically comprised of about 100 amino acids. In the signaling process, SH2 domains bind to specific phosphotyrosine motifs of target proteins (Songyang *et al.*, 1993; Escobedo *et al.*, 1991). The apoB-100 sequence was examined for presence of SH2-like regions and numerous regions in the apoB-100 sequences were found to share some commonalties with SH2 domains of signaling proteins (FIG. 3A-FIG. 3D). This suggests that apoB-100 may interact with phosphorylated proteins through SH2-like regions.

c. The SH1 Domain

Typically, signal transduction proteins also contain a kinase domain or src homology domain 1 (SH1) which is located in the carboxyl region of the protein and is comprised of about 300 amino acids (Rudd *et al.*, 1993). SH1 domains are highly homologous. Regions of apo B-100 have been found that share homology with SH1 domains (FIG. 4). In addition, apo B-100

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shares homolog with the catalytic loop or active site motif in these signaling proteins. For example, the active site motif of *lyn* (EC 2.7.1.1 12) is R₃₅₉KNYIHRDLRAAN (SEQ ID NO:52); a sequence that is highly conserved. An analogous region is found in apoB-100, K₃₉₁₉GTLAHRDFSAE (SEQ ID NO:53).

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Furthermore, apo B-100 shares amino acid sequence homolog with the activation regions located at the amino- and carboxyl- termini of signal transduction proteins (FIG. 6A and FIG. 6B). Protein Kinase C and c-AMP-dependent kinase control sites are present at the amino-terminus of signal transduction proteins. Tyrosine kinase control sites are located in the carboxyl-terminus of these proteins. Typically, there is little sequence homology, at the amino-termini, but high homology is common at the carboxyl-termini of signaling protein kinases.

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Regions of homology, within apo B-100 having sequence similarity to SH3, SH2 and SH1 domains and other cell signaling proteins, all point to the possibility that apo B-100 is involved in intracellular signaling.

5. PROTEIN EXPRESSION

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As described above, the inventors have discovered that a particular region of the apoB-100 molecule is similar in sequence to the Steroid Regulatory Element Binding Proteins, SREBP1 and 2 and ADD1. Other regions of the apoB-100 molecule are similar to specific regions in other known DNA binding proteins including, but not limited to ISGF3 γ , coiled-coil regions of GCN4 and hMLKI, and the proline-pipe sequences of Tus. Further, the inventors found that the amino acid sequence of apolipoproteins, such as apoB-100 have regions involved with nucleotide binding and nuclear localization. For example, apolipoproteins such as apoB-100 show homology to the SH1 kinase domains of protein tyrosine kinases and the HIGH and KMSK motif plus critical lysine of tRNA synthetases both known to bind ATP as well as to the basic helix-loop-helix motif of sterol regulatory element binding proteins (SREBPs) known to localize to the nucleus where they are involved in the regulation of transcription.

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a. Expression of apoB100

In certain embodiments of the present invention, it will be necessary to obtain apoB100 or lipoproteins containing apoB100 for use as DNA binding compositions. In particular embodiments as described herein below, such apoB100 may be obtained from the lipoprotein fraction of primate serum. As an alternative to purifying apoB100 from LDL fraction of serum, it is possible to generate pure fractions of apoB-100 by recombinant expression of the apoB100 gene. The apoB100 gene can be inserted into an appropriate expression system. The gene can be expressed in any number of different recombinant DNA expression systems to generate large amounts of the polypeptide product, which can then be purified and used as a DNA binding composition as described herein.

In one embodiment, specific amino acid sequence domains of an apoB100 polypeptide having for example, the sequence of SEQ ID NO:1, can be prepared. These may, for instance, be minor sequence variants of a polypeptide that arise due to natural variation within the population or they may be homologues found in other species. They also may be sequences that do not occur naturally but that are sufficiently similar that they function similarly and/or elicit an immune response that cross-reacts with natural forms of the polypeptide.

The nucleotide binding, nuclear localization and signal transduction domains of the apoB100 molecule are discussed in detail herein below. Recombinant technologies, well known to those of skill in the art, may be used to produce recombinant apoB100 with one or more of these domains having sequences that optimize the DNA binding and/or nuclear localization capacities of the molecule. Furthermore, in certain instances it may be necessary to "customize" such domains in order to increase binding to a particular DNA sequence whilst decreasing the binding to other sequences. Alternatively, it may be preferable to alter a particular apoB100 polypeptide, in order to decrease its binding affinity for a particular molecule. Accordingly, sequence variants of these domains can be prepared by standard methods of site-directed mutagenesis such as those described below in the following section.

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Amino acid sequence variants of an apoB100 polypeptide, or particular domains therein can be substitutional, insertional or deletion variants. Deletion variants lack one or more residues of the native protein which are not essential for function or immunogenic activity.

5 Substitutional variants typically contain the exchange of one amino acid for another at one or more sites within the protein, and may be designed to modulate one or more properties of the polypeptide such as stability against proteolytic cleavage. Substitutions preferably are conservative, that is, one amino acid is replaced with one of similar shape and charge. Conservative substitutions are well known in the art and include, for example, the changes of:
10 alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine; serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or
15 phenylalanine; and valine to isoleucine or leucine.

 Insertional variants include fusion proteins such as those used to allow rapid purification of the polypeptide and also can include hybrid proteins containing sequences from other proteins and polypeptides which are homologues of the polypeptide. For example, an insertional variant
20 could include portions of the amino acid sequence of the polypeptide from one species, together with portions of the homologous polypeptide from another species. Other insertional variants can include those in which additional amino acids are introduced within the coding sequence of the polypeptide. These typically are smaller insertions than the fusion proteins described above and are introduced, for example, into a protease cleavage site. Alternatively, insertional variants of the
25 present invention may be created in which one or more DNA binding domains and nuclear localization domain have been added to a native apoB100 molecule to alter particular characteristics of the molecule.

 In one embodiment, major antigenic determinants of the polypeptide are identified by an
30 empirical approach in which portions of the gene encoding the polypeptide are expressed in a recombinant host, and the resulting proteins tested for their ability to elicit an immune response.

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For example, PCR can be used to prepare a range of cDNAs encoding peptides lacking successively longer fragments of the C-terminus of the protein. The immunoprotective activity of each of these peptides then identifies those fragments or domains of the polypeptide that are essential for this activity. Further experiments in which only a small number of amino acids are removed at each iteration then allows the location of the antigenic determinants of the polypeptide.

Another embodiment for the preparation of polypeptides according to the invention is the use of peptide mimetics. Mimetics are peptide-containing molecules that mimic elements of protein secondary structure. See, for example, Johnson *et al.*, "Peptide Turn Mimetics" in *BIOTECHNOLOGY AND PHARMACY*, Pezzuto *et al.*, Eds., Chapman and Hall, New York (1993). The underlying rationale behind the use of peptide mimetics is that the peptide backbone of proteins exists chiefly to orient amino acid side chains in such a way as to facilitate molecular

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interactions, such as those of antibody and antigen. A peptide mimetic is expected to permit molecular interactions similar to the natural molecule.

Successful applications of the peptide mimetic concept have thus far focused on mimetics of β -turns within proteins, which are known to be highly antigenic. Likely β -turn structure within an polypeptide can be predicted by computer-based algorithms as discussed above. Once the component amino acids of the turn are determined, peptide mimetics can be constructed to achieve a similar spatial orientation of the essential elements of the amino acid side chains.

Modification and changes may be made in the structure of a gene and still obtain a functional molecule that encodes a protein or polypeptide with desirable characteristics. The following is a discussion based upon changing the amino acids of a protein to create an equivalent, or even an improved, second-generation molecule. The amino acid changes may be achieved by change the codons of the DNA sequence, according to the following data.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid substitutions can be made in a protein sequence, and its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the DNA sequences of genes without appreciable loss of their biological utility or activity.

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte & Doolittle, 1982).

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TABLE 1

| Amino Acids | | | Codons | | | | | |
|---------------|-----|---|--------|-----|-----|-----|-----|-----|
| Alanine | Ala | A | GCA | GCC | GCG | GCU | | |
| Cysteine | Cys | C | UGC | UGU | | | | |
| Aspartic acid | Asp | D | GAC | GAU | | | | |
| Glutamic acid | Glu | E | GAA | GAG | | | | |
| Phenylalanine | Phe | F | UUC | UUU | | | | |
| Glycine | Gly | G | GGA | GGC | GGG | GGU | | |
| Histidine | His | H | CAC | CAU | | | | |
| Isoleucine | Ile | I | AUA | AUC | AUU | | | |
| Lysine | Lys | K | AAA | AAG | | | | |
| Leucine | Leu | L | UUA | UUG | CUA | CUC | CUG | CUU |
| Methionine | Met | M | AUG | | | | | |
| Asparagine | Asn | N | AAC | AAU | | | | |
| Proline | Pro | P | CCA | CCC | CCG | CCU | | |
| Glutamine | Gln | Q | CAA | CAG | | | | |
| Arginine | Arg | R | AGA | AGG | CGA | CGC | CGG | CGU |
| Serine | Ser | S | AGC | AGU | UCA | UCC | UCG | UCU |
| Threonine | Thr | T | ACA | ACC | ACG | ACU | | |
| Valine | Val | V | GUA | GUC | GUG | GUU | | |
| Tryptophan | Trp | W | UGG | | | | | |
| Tyrosine | Tyr | Y | UAC | UAU | | | | |

It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like.

Each amino acid has been assigned a hydropathic index on the basis of their hydrophobicity and charge characteristics (Kyte & Doolittle, 1982), these are: Isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9);

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alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

5 It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.*, still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those which are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly
10 preferred.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U.S. Patent 4,554,101, incorporated herein by reference, states that the greatest local average hydrophilicity of a protein, as governed by the
15 hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U.S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4);
20 proline (-0.5 \pm 1); alanine (-0.5); histidine *-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4).

It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent and immunologically equivalent
25 protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those that are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally based on the relative similarity
30 of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing

characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

5 **b. apoB100 Variants**

10 In order to determine the optimal DNA-binding sequences, recombinant fragments of apoB-100 or other apolipoproteins may be used in mobility shift assays or other common protein-DNA interaction assays, including, but not limited to, methylation interference assays, DNase-I footprinting assays, UV-crosslinking assays, Biotin/Streptavidin affinity systems, or screening expression libraries encoding DNA-binding proteins. The recombinant apolipoprotein fragments are expressed by cloning these cDNA fragments in commercially available eukaryotic expression vectors and employing recombinant DNA expression techniques well known to the art.

15 In addition, the recombinant fragments may be mutated by employing site-directed mutagenesis or oligonucleotide-directed mutagenesis techniques in order to improve their affinity for nucleic acids and used either in their original or mutated form. Mutations in the recombinant apolipoprotein fragments may include, but are not limited to, addition of endosomolytic and/or nuclear localization peptide sequences employing common recombinant DNA technology. The recombinant protein fragments are prebound to the nucleic acids of interest prior to their reassembly into freshly isolated lipoproteins and subsequent transfection. Alternatively, they are reassembled into lipoproteins prior to *in vitro* nucleic acid binding and subsequent transfection. Separation of protein-bound DNA from free DNA may be required prior to transfection and is accomplished by adsorption to nitrocellulose membranes or other common techniques including, but not limited to size-exclusion or density ultracentrifugation.

25 Site specific mutations can be made within the proposed DNA binding motifs or nuclear localization signal sequences of the apolipoproteins described in this invention, in order to improve their homology with known DNA binding motifs (*e.g.*, SREBP-like DNA-binding motifs, ISGF3 γ -like DNA-binding motifs) and nuclear localization signal sequences (*e.g.*, NLS from human p53, Ap 1, IGFBP-3, ir, and apo J). Specific mutations in the DNA sequences of

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steroid regulatory elements (SRE) and IFN-stimulated response elements which affect the DNA-binding affinity of SREBP and ISGF3 γ , respectively, have been described (Smith *et al.*, 1990; Briggs *et al.*, 1993; Wang *et al.*, 1993; Veals *et al.*, 1992).

5 Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent proteins or peptides, through specific mutagenesis of the underlying DNA. The technique further provides a ready ability to prepare and test sequence variants, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence change(s) into the DNA. Site-specific mutagenesis allows the production
10 of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Typically, a primer of about 17 to 25 nucleotides in length is preferred, with about 5 to 10 residues on both sides of the junction of
15 the sequence being altered.

In general, the technique of site-specific mutagenesis is well known in the art. As will be appreciated, the technique typically employs a bacteriophage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis
20 include vectors such as the M13 phage. These phage vectors are commercially available and their use is generally well known to those skilled in the art. Double stranded plasmids are also routinely employed in site directed mutagenesis, which eliminates the step of transferring the gene of interest from a phage to a plasmid.

25 In general, site-directed mutagenesis is performed by first obtaining a single-stranded vector, or melting of two strands of a double stranded vector which includes within its sequence a DNA sequence encoding the desired protein. An oligonucleotide primer bearing the desired mutated sequence is synthetically prepared. This primer is then annealed with the single-stranded DNA preparation, and subjected to DNA polymerizing enzymes such as *E. coli*
30 polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated

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sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected that include recombinant vectors bearing the mutated sequence arrangement.

5 The preparation of sequence variants of the selected gene using site-directed mutagenesis is provided as a means of producing potentially useful species and is not meant to be limiting, as there are other ways in which sequence variants of genes may be obtained. For example, recombinant vectors encoding the desired gene may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants.

10 6. PURIFICATION OF LIPOPROTEINS

 The purification of plasma LDL involves obtaining a composition of Lp(a) and subjecting the composition to reductive cleavage in a manner that allows the formation of cleavage products apo (a) and apoB100. These products are then separated to yield purified apo
15 B100. Plasma lipoproteins may be isolated using standard sequential flotation ultracentrifugation methods as described (Schumaker and Puppione, 1986).

a. Purification of Lp(a)

 Lp(a) is known to be made in the liver of primates. The LDL and VLDL in the plasma
20 represents the primary source for the purification of Lp(a). Plasma may be collected from any primate source for the purposes of the invention, or indeed any other source suspected of possessing Lp(a). The Lp(a) component of the plasma can then be separated from other components of the plasma using ultracentrifugational flotation at a density of 1.21 g/mL for 20 hours at 50, 000rpm followed by affinity chromatography using lysine-Sepharose™. Of course,
25 the ultra centrifugational procedure is only exemplary and those of skill in the art will be able to vary them according to the particular equipment and study need without undue experimentation. The plasma may be supplemented with various inhibitors to prevent the Lp(a) from interacting with LDL components of the plasma.

30 Having separated Lp(a) from the other plasma components the Lp(a) sample is purified using affinity chromatography lysine-Sepharose™ chromatography. This separation is

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described in detail in PCT publication WO 97/17371, specifically incorporated herein by reference.

In some cases, it is desirable to use a method other than lysine-Sepharose™ chromatography for the purification of Lp(a), in such instances other chromatographic methods such FPLC may be employed. Such methods are disclosed in Scanu *et al.*, 1993, incorporated herein by reference, and may be used in conjunction with the present invention to purify apo B100 from Lp(a).

The product purity can be assessed by for example, mobility on, 1% agarose gels, Western blots of SDS PAGE, utilizing anti-LDL antibodies.

b. Isolation of Apo B100 from Lp (a)

(i) using centrifugation

Following the purification of Lp(a), the apoB100 may be separated from the apo A fraction of the Lp(a) complex using reductive cleavage.. The purified intact Lp(a) protein is subjected to reductive cleavage wherein a known volume of Lp(a) is incubated with a reductant. Exemplary reductants include homocysteine, N-acetyl cysteine, 2-mercaptoethanol, 3-mercaptopropionate, 2-aminoethanol, dithiothreitol, and DTE.

The reaction is incubated at room temperature for 10-20 minutes. This is followed by the addition of an inhibitor to prevent non-covalent, lysine mediated interactions between apo (a) and apoB100. ε-Aminocaproic acid (EACA) may be used as such an inhibitor. substituted by other lysine analogues, for example, compounds such as trans 4(amino-methyl)-cyclohexanecarboxylic acid, N-acetyl-L-lysine, p-benzylamine sulfonic acid, hexylamine, benzamidine, benzylamine, L-proline. Of course these are only exemplary lysine analogues and those of skill in the art may use other lysine analogues to prevent interaction between apo (a) and apoB100 proteins. The reaction conditions are described in greater detail in PCT publication number WO 97/17371. Of course, the conditions for the separation of apo (a) from the reaction mixture using sucrose density ultracentrifugation is only exemplary, and other methods commonly used by those of skill in the art may be used.

(ii) Isolation Using Chromatographic Methods

As an alternative to the above methods for the isolation of apo B100 from Lp(a) chromatographic methods may be utilized as exemplified below.

Heparin Sepharose™ Chromatography

Lp(a) may be treated with a reducing agent in the presence of a lysine analogue. For the purposes of this invention the lysine analog is supplied to prevent the interaction of apo (a) with apoB100. The reducing agent is supplied to break the disulfide bond of Lp (a). Lysine analogs for this invention include but are not limited to compounds such as EACA, trans 4(amino-methyl)-cyclohexanecarboxylic acid, N-acetyl-L-lysine, p-benzylamine sulfonic acid, hexylamine, benzamidine, benzylamine, L-proline or any other lysine analogue known to the artisan skilled in the art may be used. Example of reducing agents that may be used in this invention include, but are not limited to, homocysteine, N-acetyl cysteine, 2-mercaptoethanol, 3-mercaptopropionate, 2-aminoethanol, dithiothreitol, and DTE.

For example, the mixture of Lp (a), a reducing agent and a lysine analog is incubated for a suitable period of time in a suitable buffer of pH 7.4. A heparin-Sepharose™ column is equilibrated with a suitable buffer containing the lysine analog and the reducing agent. The mixture is applied to the equilibrated column, the column is washed with the same buffer and the first eluate is collected.

The first eluate from the column contains the apo (a) dissociated from Lp (a). The "free" apo (a) is dialyzed against an appropriate buffer. the dialysis product is pure apo (a) that may be freeze dried and stored at -20°C or used immediately. The column is further washed with the buffer for a total of three column volumes followed by 3 volumes of 2M NaCl in the buffer. The high salt concentration serves to dissociate the remaining unreacted Lp(a) and LDL containing apoB100 free of apo (a).

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Lysine-Sepharose™ Chromatography

An alternative to heparin-Sepharose™ chromatography is lysine chromatography. In this type of separation, Lp(a) is treated with a suitable reducing agent and then applied to a lysine Sepharose™ column that has been equilibrated with a suitable buffer of pH 7.4 containing the reducing agent. The column is washed with the same buffer and the first volume of elute is collected. This fraction contains LDL dissociated from apo (a). Further details of this type of chromatography for separating apolipoproteins may be found in PCT Publication WO 97/17371.

7. SCREENING NUCLEIC ACIDS THAT BIND LDL

Specifically contemplated by the present inventors are chip-based DNA technologies such as those described by Hacia *et al.* (1996) and Shoemaker *et al.* (1996). Chip technologies may be used to present DNA arrays for screening.

In a first embodiment, chip technologies may be employed to synthesize a variety of DNAs in order to test for their binding to an LDL with a specific apoB100 binding region. Briefly, these techniques involve quantitative methods for analyzing large numbers of nucleic acids rapidly and accurately. By tagging genes with oligonucleotides or using fixed probe arrays, one can employ chip technology to segregate target molecules as high density arrays and screen these molecules on the basis of hybridization. See also Pease *et al.* (1994); Fodor *et al.* (1991).

Thus, the invention may be applied for the screening of nucleic acids that bind to apoB100 containing lipoproteins. The LDL polypeptide or fragment may be either free in solution, fixed to a support, expressed in or on the surface of a cell, for example a bacterial cell. Either the LDL polypeptide or the nucleic acid may be labeled, thereby permitting determining of binding to the DNA molecules.

In another embodiment, the assay may measure the inhibition of binding of LDL to a natural or artificial substrate or binding partner. Competitive binding assays can be performed in which one of the agents (LDL, binding partner or compound) is labeled. Usually, the

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polypeptide will be the labeled species. One may measure the amount of free label versus bound label to determine binding or inhibition of binding.

Another technique for high throughput screening of compounds is described in WO 84/03564. Large numbers of small test nucleic acids (test compounds) are synthesized on a solid substrate, such as plastic pins or some other surface. Similarly, test compounds of the present invention are reacted with LDL and washed. Bound polypeptide is detected by various methods.

In an alternative embodiment, the invention may be applied for the screening for variants of apoB100 containing lipoproteins to determine a greater or lesser affinity for a particular type of nucleic acid. These screening methods would be similar to those described above, except that the LDL peptide variants will be presented as an array with the nucleic acid binding regions being used to probe the array. Currently, one of the most widely used approaches for screening polypeptide libraries is to display polypeptides on the surface of filamentous bacteriophage (Smith, 1991; Smith, 1992). Ladner *et al.*, (U.S. Patent No 5,403,484, specifically incorporated herein by reference) reported the display of proteins on the outer surface of a chosen bacterial cell, spore or phage, in order to identify and characterize binding proteins.

In an alternative embodiment, purified apoB100 or DNA-binding fragments thereof can be coated directly onto plates for use in the screening techniques. Alternatively, antibodies to the polypeptide can be used to immobilize the polypeptide to a solid phase. Also, fusion proteins containing a DNA binding region (preferably a terminal region) may be used to link peptides to a solid phase. Once linked, randomly sheared genomic DNA, transcripts or randomly generated oligomers may be contacted with the bound peptides. Any bound nucleic acid fragments can be identified by PCR using random primers if they are large enough. In the case where random oligomers are used, the oligomers, in addition to the random region, may comprise built in primer binding sites that can be used to amplify an intervening random region, thereby identifying the region binding to apoB100.

Thus, using the technologies described herein, it will be possible for one of skill in the art to screen for and isolate a variety of nucleic acids that bind to apoB100 and variants of apoB100 that exhibit nucleic acid binding capacity, including increased or decreased binding as compared to wild-type apoB100.

8. LDL-DNA COMPLEX FORMATION

In particular aspects of the present invention, lipoproteins are employed in order to transport DNA into cell *in vitro* and *in vivo*. In the present invention, optimal DNA/LDL binding has been established. In particular embodiments a 1:1 ratio of DNA:LDL protein molar ratio of 1:1 are incubated at 37 °C for 30 min in a buffered solution. An exemplary buffer may be 50 mM Tris-HCl at pH 7.4 containing 150 mM NaCl. and 10 mM MgCl₂. The concentrations of DNA and LDL protein may range from the pmolar range to the μmolar range. In a preferred embodiment, 0.39 pmole DNA are incubated with 0.39 pmole LDL-protein.

The incubation conditions may be altered to increase or decrease the efficiency of DNA/LDL binding. For example the incubation may occur at temperatures ranging from 4°C to 50°C, thus it is contemplated that the reaction mixture may be incubated at 4°C, 6°C, 8°C, 10°C, 12°C, 14°C, 16°C, 18°C, 20°C, 22°C, 24°C, 26°C, 28°C, 30°C, 32°C, 34°C, 36°C, 38°C, 40°C, 42°C, 44°C, 46°C, 48°C, 50°C.

The time of incubation may be varied from as little as 10 minutes to as long as 5 hours. Thus it is well within the skill of one in the art to incubate the mixture for varying degrees of time.

Other embodiments contemplate varying the concentration of MgCl₂ in the media. Thus the MgCl₂ concentration may vary from 1mM to 100 mM. Thus, it is contemplated that the reaction mixture contains 5mM MgCl₂, 10mM MgCl₂, 12mM MgCl₂, 15mM MgCl₂, 20mM MgCl₂, 30mM MgCl₂, 35mM MgCl₂, 40mM MgCl₂, 50mM MgCl₂, 60mM MgCl₂, 65mM MgCl₂, 70mM MgCl₂, 80mM MgCl₂, 90mM MgCl₂, or 100mM MgCl₂.

9. GENE DELIVERY AND EXPRESSION IN EUKARYOTIC CELLS

The gene delivery system of the instant invention can be used to express any gene of interest in eukaryotic cells. The gene or its cDNA sequence is cloned into a plasmid containing the specific lipoprotein binding sequences (including, but not limited to SRE, E/C, FAS) and/or any eukaryotic regulatory sequence (for example, but not limited to HCMV, or tyrosine kinase promoter region) using DNA cloning techniques well known to the art. The orientation, number and location of the lipoprotein binding sequences may vary within the nucleic acid vector, but should not interrupt the protein coding sequence of the gene of interest.

The gene delivery system of the instant invention (see FIG. 15) can be used to transfect eukaryotic cells either *in vivo* or *in vitro* with any expression vector containing one or more of the aforementioned lipoprotein binding sequences. Expression vectors are designed using recombinant DNA cloning techniques known to the art and generally include five components linked in the following 5' to 3' orientation: i) an eukaryotic promoter sequence, 2) a sequence encoding a 5' untranslated RNA (UTR) which may include a first intron sequence followed by a consensus Kozak sequence and an initiation ATG, 3) a protein coding sequence, 4) a 3' UTR, and 5) a cognate transcription terminator sequence.

Lipoproteins are isolated from blood in a manner similar to the previously described procedures (see, Example 1) and bound to the nucleic acids of interest in a manner similar to the previously described DNA binding protocol (see, Example 2). Separation of protein-bound DNA from free DNA may be required prior to transfection and can be accomplished by adsorption to nitrocellulose membranes or other techniques well known to the art including, but not limited to size-exclusion or density ultracentrifugation.

a) Control Regions

In order for the gene delivery system of the present invention to effect expression of a transcript encoding a selected gene, the polynucleotides encoding these genes will be under the transcriptional control of a promoter. A "promoter" refers to a DNA sequence recognized by the synthetic machinery of the host cell, or introduced synthetic machinery, that is required to initiate the specific transcription of a gene. The phrase "under transcriptional control" means

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that the promoter is in the correct location in relation to the polynucleotide to control RNA polymerase initiation and expression of the polynucleotide.

5 The term promoter will be used here to refer to a group of transcriptional control modules that are clustered around the initiation site for RNA polymerase II. Much of the thinking about how promoters are organized derives from analyses of several viral promoters, including those for the HSV thymidine kinase (tk) and SV40 early transcription units. These studies, augmented by more recent work, have shown that promoters are composed of discrete functional modules, each consisting of approximately 7-20 bp of DNA, and containing one or
10 more recognition sites for transcriptional activator or repressor proteins.

At least one module in each promoter functions to position the start site for RNA synthesis. The best known example of this is the TATA box, but in some promoters lacking a TATA box, such as the promoter for the mammalian terminal deoxynucleotidyl transferase gene
15 and the promoter for the SV40 late genes, a discrete element overlying the start site itself helps to fix the place of initiation.

Additional promoter elements regulate the frequency of transcriptional initiation. Typically, these are located in the region 30-110 bp upstream of the start site, although a
20 number of promoters have recently been shown to contain functional elements downstream of the start site as well. The spacing between promoter elements frequently is flexible, so that promoter function is preserved when elements are inverted or moved relative to one another. In the tk promoter, the spacing between promoter elements can be increased to 50 bp apart before activity begins to decline. Depending on the promoter, it appears that individual elements can
25 function either cooperatively or independently to activate transcription.

The particular promoter that is employed to control the expression of a therapeutic gene is not believed to be critical, so long as it is capable of expressing the polynucleotide in the targeted cell. Thus, where a human cell is targeted, it is preferable to position the
30 polynucleotide coding region adjacent to and under the control of a promoter that is capable of

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being expressed in a human cell. Generally speaking, such a promoter might include either a human or viral promoter.

In preferred embodiments, the human cytomegalovirus (CMV) immediate early gene promoter, the SV40 early promoter and the Rous sarcoma virus long terminal repeat can be used to obtain high-level expression of the polynucleotide of interest. The use of other viral or mammalian cellular or bacterial phage promoters which are well-known in the art to achieve expression of polynucleotides is contemplated as well, provided that the levels of expression are sufficient to produce a growth inhibitory effect.

By employing a promoter with well-known properties, the level and pattern of expression of a polynucleotide following transfection can be optimized. For example, selection of a promoter which is active in specific cells, such as tyrosinase (melanoma), alpha-fetoprotein and albumin (liver tumors), CC10 (lung tumor) and prostate-specific antigen (prostate tumor) will permit tissue-specific expression of the therapeutic gene.

Enhancers were originally detected as genetic elements that increased transcription from a promoter located at a distant position on the same molecule of DNA. This ability to act over a large distance had little precedent in classic studies of prokaryotic transcriptional regulation. Subsequent work showed that regions of DNA with enhancer activity are organized much like promoters. That is, they are composed of many individual elements, each of which binds to one or more transcriptional proteins.

The basic distinction between enhancers and promoters is operational. An enhancer region as a whole must be able to stimulate transcription at a distance; this need not be true of a promoter region or its component elements. On the other hand, a promoter must have one or more elements that direct initiation of RNA synthesis at a particular site and in a particular orientation, whereas enhancers lack these specificities. Promoters and enhancers are often overlapping and contiguous, often seeming to have a very similar modular organization.

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Additionally, any promoter/enhancer combination (as per the Eukaryotic Promoter Data Base EPDB) could be used to drive expression of a particular construct. Use of a T3, T7 or SP6 cytoplasmic expression system is another possible embodiment. Eukaryotic cells can support cytoplasmic transcription from certain bacteriophage promoters if the appropriate bacteriophage polymerase is provided, either as part of the delivery complex or as an additional genetic expression vector.

According to the present invention, a number of different promoters are required. It is contemplated that these promoters may be the same or different, but the selection of particular promoters for particular uses may be advantageous.

b) IRES

In certain embodiments of the invention, the use of internal ribosome binding site (IRES) elements may prove advantageous in accordance with the present invention. These elements are used to create multigene, or polycistronic, messages. IRES elements are able to bypass the ribosome scanning model of 5' methylated Cap dependent translation and begin translation at internal sites (Pelletier and Sonenberg, 1988). IRES elements from two members of the picornavirus family (polio and encephalomyocarditis) have been described (Pelletier and Sonenberg, 1988), as well an IRES from a mammalian message (Macejak and Sarnow, 1991). IRES elements can be linked to heterologous open reading frames. Multiple open reading frames can be transcribed together, each separated by an IRES, creating polycistronic messages. By virtue of the IRES element, each open reading frame is accessible to ribosomes for efficient translation. Multiple genes can be efficiently expressed using a single promoter/enhancer to transcribe a single message.

Any heterologous open reading frame can be linked to IRES elements. This includes genes for secreted proteins, multi-subunit proteins, encoded by independent genes, intracellular or membrane-bound proteins and selectable markers. In this way, expression of several proteins can be simultaneously engineered into a cell with a single construct and a single selectable marker.

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In addition, it may be desirable to include polyadenylation signals in the vectors. These signals serve to terminate transcription and to stabilize mRNA transcripts produced from the vectors. A preferred polyadenylation signal is an SV40 polyadenylation signal.

5 **c) Genes**

The present invention contemplates the use of a variety of different genes inserted into the SV40 vector. For example, genes encoding enzymes, hormones, cytokines, oncogenes, receptors, tumor suppressors, transcription factors, drug selectable markers, toxins and various antigens are contemplated as suitable genes for use according to the present invention. In addition, antisense constructs derived from oncogenes are other "genes" of interest according to the present invention.

A common gene currently being used in many gene therapy trials is p53, which currently is recognized as a tumor suppressor gene. High levels of mutant p53 have been found in many cells transformed by chemical carcinogenesis, ultraviolet radiation, and several viruses. The p53 gene is a frequent target of mutational inactivation in a wide variety of human tumors and is already documented to be the most frequently-mutated gene in common human cancers. It is mutated in over 50% of human NSCLC (Hollstein *et al.*, 1991) and in a wide spectrum of other tumors. Overexpression of wild-type p53 has been shown in some cases to be anti-proliferative in human tumor cell lines. Thus, p53 can act as a negative regulator of cell growth (Weinberg, 1991) and may directly suppress uncontrolled cell growth or indirectly activate genes that suppress this growth. It has also been reported that transfection of DNA encoding wild-type p53 into cancer cell lines restores growth suppression control in such cells (Casey *et al.*, 1991; Takahasi *et al.*, 1992). It is thus proposed that the treatment of p53-associated cancers with wild type p53 in the compositions of the present invention will reduce the number of malignant cells or their growth rate.

p16^{INK4} belongs to a newly described class of CDK-inhibitory proteins that also includes p16^B, p21^{WAF1}, and p27^{KIP1}. The p16^{INK4} gene maps to 9p21, a chromosome region frequently deleted in many tumor types. Homozygous deletions and mutations of the p16^{INK4} gene are frequent in human tumor cell lines. This evidence suggests that the p16^{INK4} gene is a tumor

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5 suppressor gene. This interpretation has been challenged, however, by the observation that the frequency of the p16^{INK4} gene alterations is much lower in primary uncultured tumors than in cultured cell lines (Caldas *et al.*, 1994; Cheng *et al.*, 1994; Hussussian *et al.*, 1994; Kamb *et al.*, 1994; Kamb *et al.*, 1994; Mori *et al.*, 1994; Okamoto *et al.*, 1994; Nobori *et al.*, 1995; Orlow *et al.*, 1994; Arap *et al.*, 1995). Restoration of wild-type p16^{INK4} function by transfection with a plasmid expression vector reduced colony formation by some human cancer cell lines (Okamoto, 1994; Arap, 1995).

10 Cell adhesion molecules, or CAM's are known to be involved in a complex network of molecular interactions that regulate organ development and cell differentiation (Edelman, 1985). Recent data indicate that aberrant expression of CAM's maybe involved in the tumorigenesis of several neoplasms: for example, decreased expression of E-cadherin, which is predominantly expressed in epithelial cells, is associated with the progression of several kinds of neoplasms (Edelman and Crossin, 1991; Frixen *et al.*, 1991; Bussemakers *et al.*, 1992; 15 Matura *et al.*, 1992; Umbas *et al.*, 1992). Also, Giancotti and Ruoslahti (1990) demonstrated that increasing expression of $\alpha_5\beta_1$ integrin by gene transfer can reduce tumorigenicity of Chinese hamster ovary cells *in vivo*. C-CAM now has been shown to suppress tumors growth *in vitro* and *in vivo*. Thus, the compositions of the present invention can be employed to mediated C-CAM suppression of tumor cell growth.

20 Other tumor suppressors that may be employed according to the present invention include RB, APC, DCC, NF-1, NF-2, WT-1, MEN-I, MEN-II, zac1, p73, VHL, MMAC1, FCC and MCC. Inducers of apoptosis, such as Bax, Bak, Bcl-X_s, Bik, Bid, Harakiri, Ad E1B, Bad and ICE-CED3 proteases, similarly could find use according to the present invention.

25 Various enzyme genes are of interest according to the present invention. Such enzymes include cytosine deaminase, hypoxanthine-guanine phosphoribosyltransferase, galactose-1-phosphate uridylyltransferase, phenylalanine hydroxylase, glucocerebrosidase, sphingomyelinase, α -L-iduronidase, glucose-6-phosphate dehydrogenase, HSV thymidine kinase and human 30 thymidine kinase.

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In another example, the expression vector may include a nucleotide sequence encoding for functional apolipoprotein A-I for the prevention or treatment of arteriosclerosis. Arteriosclerosis is a disease that is characterized by the development of arteriosclerotic lesions which contain cholesterol esters and other lipids that are derived from the blood circulation.

5 The plasma concentration of HDL is inversely correlated with the risk for development of arteriosclerosis. HDL present in the blood circulation take up free cholesterol from extrahepatic cells which through the action of LCAT (lecithin-cholesterol acyltransferase) is converted to cholesterol esters and stored in the core of the HDL particles. The HDL cholesterol esters are transported either directly or indirectly *via* transfer to triglyceride rich lipoproteins (*i.e.*, VLDL,

10 IDL, LDL) to the liver by a process called "reverse cholesterol transport". Reverse cholesterol transport is of great importance for maintaining cholesterol homeostasis since the liver is the major organ for cholesterol excretion from the body *via* bile acids. Apo A-I is the major protein constituent of HDL and a cofactor LCAT. Therefore, increasing the plasma concentration of apo A-I containing HDL can increase the reverse cholesterol transport and reduce the risk for

15 arteriosclerosis.

Hormones are another group of gene that may be used in the SV40 vectors described herein. Included are growth hormone, prolactin, placental lactogen, luteinizing hormone, follicle-stimulating hormone, chorionic gonadotropin, thyroid-stimulating hormone, leptin,

20 adrenocorticotropin (ACTH), angiotensin I and II, β -endorphin, β -melanocyte stimulating hormone (β -MSH), cholecystokinin, endothelin I, galanin, gastric inhibitory peptide (GIP), glucagon, insulin, lipotropins, neurophysins, somatostatin, calcitonin, calcitonin gene related peptide (CGRP), β -calcitonin gene related peptide, hypercalcemia of malignancy factor (1-40), parathyroid hormone-related protein (107-139) (PTH-rP), parathyroid hormone-related protein

25 (107-111) (PTH-rP), glucagon-like peptide (GLP-1), pancreastatin, pancreatic peptide, peptide YY, PHM, secretin, vasoactive intestinal peptide (VIP), oxytocin, vasopressin (AVP), vasotocin, enkephalinamide, metorphinamide, alpha melanocyte stimulating hormone (alpha-MSH), atrial natriuretic factor (5-28) (ANF), amylin, amyloid P component (SAP-1), corticotropin releasing hormone (CRH), growth hormone releasing factor (GHRH), luteinizing

30 hormone-releasing hormone (LHRH), neuropeptide Y, substance K (neurokinin A), substance P and thyrotropin releasing hormone (TRH).

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Other classes of genes that are contemplated to be inserted into the SV40 vectors of the present invention include interleukins and cytokines. Interleukin 1 (IL-1), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11 IL-12, GM-CSF and G-CSF.

5

Other therapeutics genes might include genes encoding antigens such as viral antigens, bacterial antigens, fungal antigens or parasitic antigens. Viruses include picornavirus, coronavirus, togavirus, flavivirus, rhabdovirus, paramyxovirus, orthomyxovirus, bunyavirus, arenavirus, reovirus, retrovirus, papovavirus, parvovirus, herpesvirus, poxvirus, hepadnavirus, and spongiform virus. Preferred viral targets include influenza, herpes simplex virus 1 and 2, measles, small pox, polio or HIV. Pathogens include trypanosomes, tapeworms, roundworms, helminths, . Also, tumor markers, such as fetal antigen or prostate specific antigen, may be targeted in this manner. Preferred examples include HIV env proteins and hepatitis B surface antigen. Administration of a vector according to the present invention for vaccination purposes would require that the vector-associated antigens be sufficiently non-immunogenic to enable long term expression of the transgene, for which a strong immune response would be desired. Preferably, vaccination of an individual would only be required infrequently, such as yearly or biennially, and provide long term immunologic protection against the infectious agent.

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In yet another embodiment, the heterologous gene may include a single-chain antibody. Methods for the production of single-chain antibodies are well known to those of skill in the art. The skilled artisan is referred to U.S. Patent No. 5,359,046, (incorporated herein by reference) for such methods. A single chain antibody is created by fusing together the variable domains of the heavy and light chains using a short peptide linker, thereby reconstituting an antigen binding site on a single molecule.

25

Single-chain antibody variable fragments (Fvs) in which the C-terminus of one variable domain is tethered to the N-terminus of the other via a 15 to 25 amino acid peptide or linker, have been developed without significantly disrupting antigen binding or specificity of the binding (Bedzyk *et al.*, 1990; Chaudhary *et al.*, 1990). These Fvs lack the constant regions (Fc) present in the heavy and light chains of the native antibody.

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Antibodies to a wide variety of molecules are contemplated, such as oncogenes, toxins, hormones, enzymes, viral or bacterial antigens, transcription factors or receptors.

5 **d. Antisense**

The instant invention can be used to transfect eukaryotic cells with ribonucleotide sequences including anti-sense RNA and ribozymes, that function to inhibit the translation of any mRNA of interest, either by direct binding (to the mRNA of interest), or blocking deoxyribonucleic acid (DNA) coding sequences preventing transcription.

10 Anti-sense RNA inhibits the translation of mRNA by direct binding to the mRNA of interest and preventing protein translation, either by inhibition of ribosome binding or the translocation of the targeted mRNA molecule which then becomes more susceptible to nuclease degradation.

15 Antisense methodology takes advantage of the fact that nucleic acids tend to pair with "complementary" sequences. By complementary, it is meant that polynucleotides are those which are capable of base-pairing according to the standard Watson-Crick complementarity rules. That is, the larger purines will base pair with the smaller pyrimidines to form combinations of guanine paired with cytosine (G:C) and adenine paired with either thymine (A:T) in the case of DNA, or adenine paired with uracil (A:U) in the case of RNA. Inclusion of less common bases such as inosine, 5-methylcytosine, 6-methyladenine, hypoxanthine and others in hybridizing sequences does not interfere with pairing. Oncogenes such as *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl* and *abl* also are suitable targets for antisense constructs.

25 Targeting double-stranded (ds) DNA with polynucleotides leads to triple-helix formation; targeting RNA will lead to double-helix formation. Antisense polynucleotides, when introduced into a target cell, specifically bind to their target polynucleotide and interfere with transcription, RNA processing, transport, translation and/or stability. Antisense RNA constructs, or DNA encoding such antisense RNA's, may be employed to inhibit gene

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transcription or translation or both within a host cell, either in vitro or in vivo, such as within a host animal, including a human subject.

Antisense constructs may be designed to bind to the promoter and other control regions, exons, introns or even exon-intron boundaries of a gene. It is contemplated that the most effective antisense constructs will include regions complementary to intron/exon splice junctions. Thus, it is proposed that a preferred embodiment includes an antisense construct with complementarity to regions within 50-200 bases of an intron-exon splice junction. It has been observed that some exon sequences can be included in the construct without seriously affecting the target selectivity thereof. The amount of exonic material included will vary depending on the particular exon and intron sequences used. One can readily test whether too much exon DNA is included simply by testing the constructs *in vitro* to determine whether normal cellular function is affected or whether the expression of related genes having complementary sequences is affected.

As stated above, "complementary" or "antisense" means polynucleotide sequences that are substantially complementary over their entire length and have very few base mismatches. For example, sequences of fifteen bases in length may be termed complementary when they have complementary nucleotides at thirteen or fourteen positions. Naturally, sequences which are completely complementary will be sequences which are entirely complementary throughout their entire length and have no base mismatches. Other sequences with lower degrees of homology also are contemplated. For example, an antisense construct which has limited regions of high homology, but also contains a non-homologous region (*e.g.*, ribozyme) could be designed. These molecules, though having less than 50% homology, would bind to target sequences under appropriate conditions.

It may be advantageous to combine portions of genomic DNA with cDNA or synthetic sequences to generate specific constructs. For example, where an intron is desired in the ultimate construct, a genomic clone will need to be used. The cDNA or a synthesized polynucleotide may provide more convenient restriction sites for the remaining portion of the construct and, therefore, would be used for the rest of the sequence.

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e. **Ribozymes**

Ribozymes are RNA molecules that catalyze the specific cleavage of RNA. Ribozyme activity is mediated through the hybridization of the ribozyme molecule to a specific sequence in the target RNA, followed by the endonucleolytic cleavage of the target RNA within that sequence. Potential RNA cleavage sites can be identified by searching for specific ribonucleotide sequences that include sequences such as GUU, GUC, and GUA within the target RNA. Hammerhead motif ribozyme molecules can then be designed that contain short RNA sequences (15-25 ribonucleotides) that are complementary to the region including the cleavage site of the target RNA.

Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cook, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cook *et al.*, 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cook *et al.*, 1981). For example, U.S. Patent No. 5,354,855 reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus, sequence-specific ribozyme-mediated inhibition of gene expression may be particularly suited to therapeutic applications (Scanlon *et al.*, 1991; Sarver *et al.*, 1990). Recently, it was reported that ribozymes elicited genetic changes in some cells lines to which they were applied; the altered genes included the oncogenes H-ras, c-fos and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon that is cleaved by a specific ribozyme.

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Since the secondary structure of both target RNA as well as the anti-sense RNA is of great importance for the hybridization of both molecules, the predicted structural features can be analyzed and RNase protection assays can be used to determine hybridization efficiency. Anti-sense RNA and ribozymes can be synthesized employing chemical nucleic acid synthesis techniques well known to the art (*i.e.*, solid phase phosphorimidite synthesis) or the RNA molecules can be produced by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense RNA. DNA sequences encoding ribozymes or anti-sense RNA may be incorporated into an expression vector. The expression vector may be prebound to purified plasma lipoprotein fractions prior to transfection into eukaryotic cells.

f. Self-initiating and self-sustaining gene expression systems

The invention gene delivery system can also be used to delivery self-initiating and self-sustaining gene expression systems. Self-initiating and self-sustaining gene expression systems may be constructed by binding a RNA polymerase to a DNA construct *in vitro* prior to the introduction of the polynucleotide into the cell as described by Wagner *et al.* (U.S. Patent No. #5,591,601). The RNA polymerase is bound to a DNA construct containing a cognate promoter of the RNA polymerase operably linked to a DNA sequence encoding for the RNA polymerase.

The expression of functional RNA polymerase in turn enables the expression of any gene of interest that contains a cognate promoter sequence recognized by the same RNA polymerase in eukaryotic host cells. DNA sequences encoding for both RNA polymerase and gene product of interest (*i.e.*, protein of interest) may be contained within the same gene expression system. The gene expression system may be prebound to purified plasma lipoprotein fractions prior to transfection into eukaryotic cells.

g. Delivery of DNA to cells *in vivo*

The invention gene delivery system can also be used to deliver DNA to cells *in vivo*. An expression vector containing the polynucleotide sequences of the gene of interest (*e.g.*, reporter gene or a healthy copy of a defective gene) is prebound to LDL according to the protocols described herein. This DNA-LDL complex is then introduced into an organism for example, a rat, mouse or human by, for example, intravenous injection. At varying times post-injection,

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LDL is isolated from the blood and probed for DNA sequences of the type that were prebound to the LDL using standard molecular biological techniques such as, but not limited to, Southern blot hybridization or PCR™.

5 The LDL also can be immunoprecipitated with anti-LDL antibodies and then probed for specific DNA sequences bound to it. In order to determine cellular internalization and/or integration of the reporter gene sequences into the genomic DNA of cells of different tissues, total genomic DNA can be isolated from various tissues (according to standard molecular biology techniques) and probed for the presence of the reporter gene sequences using specific
10 polynucleotide probes in PCR™ or Southern blot hybridization techniques. In addition, total cellular RNA can be isolated from various different tissues using standard molecular biology techniques and probed for the presence of specific mRNA encoded for by the reporter gene polynucleotide sequences using specific antisense polynucleotide probes in Northern blot hybridization techniques or ribonuclease (RNase) protection assays.

15 Expression of a functional protein encoded for by the gene of interest in different tissues can be analyzed using techniques well known to the art, such as. Western blot hybridization of cellular protein extracts with antibodies that bind specifically to the reporter gene product (i.e., protein of interest) or direct detection of intracellular fluorescence (e.g., when reporter genes are
20 used that encode for blue or green fluorescent proteins (e.g., GFP from Clontech Inc.).

 Several non-viral methods for the transfer of a DNA-LDL complex of the present invention into cultured mammalian cells also are contemplated by the present invention. These include calcium phosphate precipitation (Graham and Van Der Eb, 1973; Chen and Okayama, 1987; Rippe *et al.*, 1990) DEAE-dextran (Gopal, 1985), electroporation (Tur-Kaspa *et al.*, 1986; Potter *et al.*, 1984), direct microinjection (Harland and Weintraub, 1985), DNA-loaded liposomes (Nicolau and Sene, 1982; Fraley *et al.*, 1979) and lipofectamine-DNA complexes, cell sonication (Fechheimer *et al.*, 1987), gene bombardment using high velocity microprojectiles (Yang *et al.*, 1990), and receptor-mediated transfection (Wu and Wu, 1987; Wu and Wu, 1988). Some of these techniques may be successfully adapted for *in vivo* or *ex vivo* use.

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Once the DNA-LDL complex has been delivered into the cell, the nucleic acid encoding the gene of interest may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the gene may be stably integrated into the genome of the cell. This
5 integration may be in the cognate location and orientation via homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the
10 host cell cycle. How the DNA-LDL complex is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of DNA molecule bound to the LDL.

In one embodiment of the invention, the DNA-LDL complex may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of
15 the methods mentioned above which physically or chemically permeabilize the cell membrane. This is particularly applicable for transfer *in vitro* but it may be applied to *in vivo* use as well. Dubensky *et al.*, (1984) successfully injected polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Neshif (1986) also demonstrated that
20 direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA-LDL complex into
25 cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The
30 microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

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Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e.*, *ex vivo* treatment. Again, DNA encoding a particular gene may be delivered via this method and still be incorporated by the present invention.

In a further embodiment of the invention, the DNA-LDL complex may be entrapped in a liposome. Liposomes are vesicular structures characterized by a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh and Bachhawat, 1991). Also contemplated are lipofectamine-DNA complexes.

Liposome-mediated nucleic acid delivery and expression of foreign DNA *in vitro* has been very successful. Wong *et al.*, (1980) demonstrated the feasibility of liposome-mediated delivery and expression of foreign DNA in cultured chick embryo, HeLa and hepatoma cells. Nicolau *et al.*, (1987) accomplished successful liposome-mediated gene transfer in rats after intravenous injection.

In certain embodiments of the invention, the liposome may be complexed with a hemagglutinating virus (HVJ). This has been shown to facilitate fusion with the cell membrane and promote cell entry of liposome-encapsulated DNA (Kaneda *et al.*, 1989). In other embodiments, the liposome may be complexed or employed in conjunction with nuclear non-histone chromosomal proteins (HMG-1) (Kato *et al.*, 1991). In yet further embodiments, the liposome may be complexed or employed in conjunction with both HVJ and HMG-1. In that such expression constructs have been successfully employed in transfer and expression of nucleic acid *in vitro* and *in vivo*, then they are applicable for the present invention. Where a bacterial promoter is employed in the DNA construct, it also will be desirable to include within the liposome an appropriate bacterial polymerase.

Other DNA-LDL complexes which can be employed to deliver a nucleic acid encoding a particular gene into cells are receptor-mediated delivery vehicles. These take advantage of the selective uptake of macromolecules by receptor-mediated endocytosis in almost all eukaryotic cells. Because of the cell type-specific distribution of various receptors, the delivery can be highly specific (Wu and Wu, 1993).

Receptor-mediated gene targeting vehicles generally consist of two components: a cell receptor-specific ligand and a DNA-binding agent. Several ligands have been used for receptor-mediated gene transfer. The most extensively characterized ligands are asialoorosomucoid (ASOR) (Wu and Wu, 1987) and transferrin (Wagner *et al.*, 1990). Recently, a synthetic neoglycoprotein, which recognizes the same receptor as ASOR, has been used as a gene delivery vehicle (Ferkol *et al.*, 1993; Perales *et al.*, 1994) and epidermal growth factor (EGF) has also been used to deliver genes to squamous carcinoma cells (Myers, EPO 0273085).

In other embodiments, the delivery vehicle may comprise a ligand and a liposome. For example, Nicolau *et al.*, (1987) employed lactosyl-ceramide, a galactose-terminal asialganglioside, incorporated into liposomes and observed an increase in the uptake of the insulin gene by hepatocytes. Thus, it is feasible that a nucleic acid encoding a particular gene also may be specifically delivered into a cell type such as lung, epithelial or tumor cells, by any number of receptor-ligand systems with or without liposomes. For example, epidermal growth factor (EGF) may be used as the receptor for mediated delivery of a nucleic acid encoding a gene in many tumor cells that exhibit upregulation of EGF receptor. Mannose can be used to target the mannose receptor on liver cells. Also, antibodies to CD5 (CLL), CD22 (lymphoma), CD25 (T-cell leukemia) and MAA (melanoma) can similarly be used as targeting moieties.

In certain embodiments, gene transfer may more easily be performed under *ex vivo* conditions. *Ex vivo* gene therapy refers to the isolation of cells from an animal, the delivery of a nucleic acid into the cells *in vitro*, and then the return of the modified cells back into an animal. This may involve the surgical removal of tissue/organs from an animal or the primary culture of

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cells and tissues. Anderson *et al.*, U.S. Patent 5,399,346, and incorporated herein in its entirety, disclose *ex vivo* therapeutic methods.

10. PHARMACEUTICAL

5 The gene delivery system of the instant invention can be administered *in vivo* in various ways including, but not limited to, intravenous, pharyngeal, epidermal, intramuscular, intraperitoneal (IP), nasal, and/or rectal. The gene delivery system of the instant invention can also be used for *in vitro* transfections of eukaryotic cell types which possess specific lipoprotein receptors on their cytoplasmic membranes, but is not limited to these cell types.

10 Pharmaceutical products that may spring from the current invention may comprise naked polynucleotide containing single or multiple copies of the specific nucleotide sequences that bind to specific DNA-binding sites of the apolipoproteins present on plasma lipoproteins as described in the current invention. The polynucleotide may encode a biologically active
15 peptide, antisense RNA, or ribozyme and will be provided in a physiologically acceptable administrable form.

Another pharmaceutical product that may spring from the current invention may comprise a highly purified plasma lipoprotein fraction, isolated according to the methodology,
20 described herein from either the patients blood or other source, and a polynucleotide containing single or multiple copies of the specific nucleotide sequences that bind to specific DNA-binding sites of the apolipoproteins present on plasma lipoproteins, prebound to the purified lipoprotein fraction in a physiologically acceptable, administrable form.

25 Yet another pharmaceutical product may comprise a highly purified plasma lipoprotein fraction which contains recombinant apolipoprotein fragments containing single or multiple copies of specific DNA-binding motifs, prebound to a polynucleotide containing single or multiple copies of the specific nucleotide sequences, in a physiologically acceptable administrable form. Yet another pharmaceutical product may comprise a highly purified
30 plasma lipoprotein fraction which contains recombinant apolipoprotein fragments containing single or multiple copies of specific DNA-binding motifs, prebound to a polynucleotide

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containing single or multiple copies of the specific nucleotide sequences, in a physiologically acceptable administrable form.

5 The dosage to be administered depends to a great extent on the body weight and physical condition of the subject being treated as well as the route of administration and frequency of treatment. A pharmaceutical composition comprising the naked polynucleotide prebound to a highly purified lipoprotein fraction may be administered in amounts ranging from 1 μ g to 1 mg polynucleotide and 1 μ g to 100 mg protein.

10 Administration of the therapeutic virus particle to a patient will follow general protocols for the administration of chemotherapeutics, taking into account the toxicity, if any, of the vector. It is anticipated that the treatment cycles would be repeated as necessary. It also is contemplated that various standard therapies, as well as surgical intervention, may be applied in combination with the described gene therapy.

15 Where clinical application of a gene therapy is contemplated, it will be necessary to prepare the complex as a pharmaceutical composition appropriate for the intended application. Generally this will entail preparing a pharmaceutical composition that is essentially free of pyrogens, as well as any other impurities that could be harmful to humans or animals. One also
20 will generally desire to employ appropriate salts and buffers to render the complex stable and allow for complex uptake by target cells.

Aqueous compositions of the present invention comprise an effective amount of the compound, dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium.
25 Such compositions can also be referred to as inocula. The phrases "pharmaceutically or pharmacologically acceptable" refer to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption
30 delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is

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incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients also can be incorporated into the compositions.

The compositions of the present invention may include classic pharmaceutical preparations. Dispersions also can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

i) Disease States

A wide variety of disease states may be treated with compositions according to the present invention. In essence, any disease that can be treated by provision of a protein or nucleic acid is amenable to this approach. Disease states include a variety of genetic abnormalities such as diabetes, cancer, cystic fibrosis and various other diseases that could be treated by increasing or decreasing expression of a protein in a target cell.

Depending on the particular disease to be treated, administration of therapeutic compositions according to the present invention will be via any common route so long as the target tissue is available via that route. This includes oral, nasal, buccal, rectal, vaginal or topical. Topical administration would be particularly advantageous for treatment of skin cancers. Alternatively, administration will be by orthotopic, intradermal, subcutaneous, intramuscular, intraperitoneal or intravenous injection. Such compositions would normally be administered as pharmaceutically acceptable compositions that include physiologically acceptable carriers, buffers or other excipients.

In certain embodiments, *ex vivo* therapies also are contemplated. *Ex vivo* therapies involve the removal, from a patient, of target cells. The cells are treated outside the patient's body and then returned. One example of *ex vivo* therapy would involve a variation of autologous bone marrow transplant. Many times, ABMT fails because some cancer cells are present in the withdrawn bone marrow, and return of the bone marrow to the treated patient results in repopulation of the patient with cancer cells. In one embodiment, however, the withdrawn bone marrow cells could be treated while outside the patient with an LDL-DNA

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particle that targets and kills the cancer cell. Once the bone marrow cells are "purged," they can be reintroduced into the patient.

The treatments may include various "unit doses." Unit dose is defined as containing a predetermined-quantity of the therapeutic composition calculated to produce the desired responses in association with its administration, *i.e.*, the appropriate route and treatment regimen. The quantity to be administered, and the particular route and formulation, are within the skill of those in the clinical arts. Also of import is the subject to be treated, in particular, the state of the subject and the protection desired. A unit dose need not be administered as a single injection but may comprise continuous infusion over a set period of time. Unit dose of the present invention may conveniently may be described in terms of 0.01mg DNA/kg body weight to 0.4mg DNA/kg body weight, with ranges in between these being contemplated such that 0.05, 0.10, 0.15, 0.20, 0.25, 0.5mg/DNA/kg body weight are administered. Likewise the amount of LDL delivered can vary from about 0.2 to about 8.0 mg/kg body weight. Thus in particular embodiments, 0.4 mg, 0.5 mg, 0.8 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 4.0 mg, 5.0 mg, 5.5 mg, 6.0 mg, 6.5 mg, 7.0 mg and 7.5 mg of LDL may be delivered to an individual *in vivo*. The dosage of DNA:LDL to be administered depends to a great extent on the weight and physical condition of the subject being treated as well as the route of administration and the frequency of treatment. A pharmaceutical composition comprising the naked polynucleotide prebound to a highly purified lipoprotein fraction may be administered in amounts ranging from 1 μ g to 1mg polynucleotide to 1 μ g to 100mg protein. Thus, particular compositions may comprise 1 μ g, 5 μ g, 10 μ g, 20 μ g, 30 μ g, 40 μ g, 50 μ g, 60 μ g, 70 μ g, 80 μ g, 100 μ g, 150 μ g, 200 μ g, 250 μ g, 500 μ g, 600 μ g, 700 μ g, 800 μ g, 900 μ g or 1000 μ g polynucleotide that is bound independently to 1 μ g, 5 μ g, 10 μ g, 20 μ g, 3.0 μ g, 40 μ g 50 μ g, 60 μ g, 70 μ g, 80 μ g, 100 μ g, 150 μ g, 200 μ g, 250 μ g, 500 μ g, 600 μ g, 700 μ g, 800 μ g, 900 μ g or 1000 μ g, 1.5mg, 5 mg, 10 mg, 20mg, 30mg, 40mg, 50mg, 60 mg, 70mg, 80 mg, 90 mg or 100mg lipoprotein. Any amount of polynucleotide may be bound to any other amount of lipoprotein to achieve the pharmaceutical concentrations of the present invention.

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ii) Cancer

One of the preferred embodiments of the present invention involves the use of the LDL vectors to deliver therapeutic genes to cancer cells. Target cancer cells include cancers of the lung, brain, prostate, kidney, liver, ovary, breast, skin, stomach, esophagus, head & neck, testicles, colon, cervix, lymphatic system and blood. Of particular interest are non-small cell lung carcinomas including squamous cell carcinomas, adenocarcinomas and large cell undifferentiated carcinomas.

According to the present invention, one may treat the cancer by directly injection a tumor with the LDL vector. Alternatively, the tumor may be infused or perfused with the vector using any suitable delivery vehicle. Local or regional administration, with respect to the tumor, also is contemplated. Finally, systemic administration may be performed. Continuous administration also may be applied where appropriate, for example, where a tumor is excised and the tumor bed is treated to eliminate residual, microscopic disease. Delivery via syringe or catheterization is preferred. Such continuous perfusion may take place for a period from about 1-2 hours, to about 2-6 hours, to about 6-12 hours, to about 12-24 hours, to about 1-2 days, to about 1-2 weeks or longer following the initiation of treatment. Generally, the dose of the therapeutic composition via continuous perfusion will be equivalent to that given by a single or multiple injections, adjusted over a period of time during which the perfusion occurs.

For tumors of ≥ 4 cm, the volume to be administered will be about 4-10 ml (preferably 10 ml), while for tumors of < 4 cm, a volume of about 1-3 ml will be used (preferably 3 ml). Multiple injections delivered as single dose comprise about 0.1 to about 0.5 ml volumes. The LDL-DNA particles may advantageously be contacted by administering multiple injections to the tumor, spaced at approximately 1 cm intervals.

In certain embodiments, the tumor being treated may not, at least initially, be resectable. Treatments with therapeutic constructs may increase the resectability of the tumor due to shrinkage at the margins or by elimination of certain particularly invasive portions. Following treatments, resection may be possible. Additional treatments subsequent to resection will serve to eliminate microscopic residual disease at the tumor site.

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A typical course of treatment, for a primary tumor or a post-excision tumor bed, will involve multiple doses. Typical primary tumor treatment involves a 6 dose application over a two week period. The two week regimen may be repeated one, two, three, four, five, six or more times. During a course of treatment, the need to complete the planned dosings may be reevaluated.

Cancer therapies also include a variety of combination therapies with both chemical and radiation based treatments. Combination chemotherapies include, for example, cisplatin (CDDP), carboplatin, procarbazine, mechlorethamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, bisulfan, nitrosurea, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicomycin, mitomycin, etoposide (VP16), tamoxifen, taxol, transplatinum, 5-fluorouracil, vincristin, vinblastin and methotrexate.

Combination radiation therapies may be x- and γ -irradiation. Dosage ranges for x-irradiation range from daily doses of 2000 to 6000 roentgens for prolonged periods of time (3 to 4 weeks), to single doses of 2000 to 6000 roentgens. Dosages for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by neoplastic cells.

Various combinations may be employed, gene therapy is "A" and the radio- or chemotherapeutic agent is "B":

A/B/A B/A/B B/B/A A/A/B A/B/B B/A/A A/B/B/B B/A/B/B

B/B/B/A B/B/A/B A/A/B/B A/B/A/B A/B/B/A B/B/A/A

B/A/B/A B/A/A/B A/A/A/B B/A/A/A A/B/A/A A/A/B/A

The terms "contacted" and "exposed," when applied to a cell, are used herein to describe the process by which a therapeutic construct and a chemotherapeutic or radiotherapeutic agent

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are delivered to a target cell or are placed in direct juxtaposition with the target cell. To achieve cell killing or stasis, both agents are delivered to a cell in a combined amount effective to kill the cell or prevent it from dividing.

5 The therapeutic compositions of the present invention are advantageously administered in the form of injectable compositions either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. These preparations also may be emulsified. A typical composition for such purpose comprises a pharmaceutically acceptable carrier. For instance, the composition may contain 10 mg, 25 mg,
10 50 mg or up to about 100 mg of human serum albumin per milliliter of phosphate buffered saline.

Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like. Examples of non-aqueous
15 solvents are propylene glycol, polyethylene glycol, vegetable oil and injectable organic esters such as ethyloleate. Aqueous carriers include water, alcoholic/aqueous solutions, saline solutions, parenteral vehicles such as sodium chloride, Ringer's dextrose, etc. Intravenous vehicles include fluid and nutrient replenishers. Preservatives include antimicrobial agents, anti-oxidants, chelating agents and inert gases. The pH and exact concentration of the various
20 components the pharmaceutical composition are adjusted according to well known parameters.

Additional formulations are suitable for oral administration. Oral formulations include such typical excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. The
25 compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders. When the route is topical, the form may be a cream, ointment, salve or spray.

11. EXAMPLES

30 The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in

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the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

MATERIALS AND METHODS

1. Isolation of Plasma Lipoproteins

Restriction endonucleases were purchased from Life Technologies, and Protease inhibitors (*i.e.*, leupeptin, PMSF, and Trasylol) were purchased from Sigma Chemical Company. Plasma lipoproteins were isolated using standard sequential flotation ultracentrifugation methods as described (Schumaker and Puppione, 1986). Throughout the entire procedure samples were kept on ice or at 4°C unless otherwise stated.

Subjects were fasted for at least 4 h prior to the start of the experimental procedures. Blood was drawn into sterile, vacuumed glass tubes containing anticoagulants, *e.g.*, 0.1% (ethylenedinitrolo)-tetracetic acid (EDTA) or heparin. Plasma was obtained by centrifugation (10 minutes at 3000 × g) and immediately adjusted to 0.005% phenylmethanesulfonyl fluoride (PMSF), 10KIU Trasylol/ml, and 1 µg leupeptin/ml. VLDL, LDL, and HDL fractions were isolated by sequential flotation ultracentrifugation for 18 h at 40,000 rpm in a Beckmann centrifuge Model LS-80M after plasma samples were adjusted with potassium bromide (ICBr) to solution densities of 1.006, 1.019, and 1.215 g/ml respectively. Immediately following ultracentrifugation, individual lipoprotein fractions were collected and dialyzed extensively against phosphate buffered saline (pH 7.4) containing 0.001% sodium azide. Protein concentrations were determined using standard BCA protein assays (Pierce Chemical Company).

2. Dna-Binding Protocol

Lipoproteins and DNA were mixed together and incubated for 30 min at room temperature in 50 mmole/liter Tris (pH 7.4), 100-154 mmoles/liter sodium chloride (NaCl), 15

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mmoles/liter magnesium chloride (MgCl_2). 6X Sample loading buffer (30% glycerol, 0.25% Xylene cyanole FF, 0.25% bromophenol blue) was added to the samples in a 1:5 V/V ratio. Samples were underloaded into 30 μl wells at the cathode edge of an 0.8% agarose gel containing 1 μg ethidium bromide/ml in Tris-Acetate buffer (pH 7.85) and electrophoresis was accomplished using 100 Volt constant until the negatively charged tracking dye had migrated at least 50% of distance from the loading well to the anodic edge of the gel.

3. Agarose Electrophoretogram of Human Lipoproteins

Agarose electrophoresis of human lipoproteins has been performed to illustrating the differential migration patterns of lipoprotein fractions VLDL, LDL, and HDL isolated from human plasma resolved using non-denaturing conditions.

Plasma lipoproteins were isolated from human blood according to the protocol described above. 6X Sample loading buffer (30% glycerol, 0.25% Xylene cyanole FF, 0.25% bromophenol blue) was added to the samples in a 1:5 V/V ratio. Samples were underloaded into 30 μl wells at the cathode edge of an 0.8% agarose gel in Tris-Acetate buffer (pH 7.85) and electrophoresis was accomplished using 100 Volt constant until the negatively charged tracking dye had migrated at least 50% of the distance from the loading well to the anodic edge of the gel.

Following electrophoresis, the agarose gel was stained for protein in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomassie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs). Lane 1 contained human VLDL (10 μg protein), Lane 2 contained human LDL (35 μg protein), and Lane 3 contained human HDL (35 μg protein). Results illustrated the differential migration of lipoprotein fractions, VLDL, LDL, and HDL, isolated from human plasma resolved using non-denaturing conditions by agarose gel electrophoresis. Lipoproteins were visualized using a protein binding dye, Coomassie Brilliant Blue (CBB). The absence of other bands in each lane indicated the high degree of purity for each lipoprotein.

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4. Radioisotope Labeling of Deoxyoligonucleotides

Complementary single stranded oligonucleotides were mixed (10 µg each) and incubated at 85°C for 5 min in 10 mM Tris HCl (pH 7.4). Immediately following incubation, the samples were cooled down slowly to room temperature to obtain double stranded oligonucleotides. The double stranded oligonucleotides were then digested with *Bam*HI and *Eco*RI for 1 h at 37°C in 50 mM Tris HCl (pH 8.0), 100 mM NAG1, and 10 mM MgCl₂. Digested double stranded oligonucleotides were purified using a Qiaquick nucleotide removal kit from Qiagen Inc. according to manufacturer's protocol. The 5' protruding ends of the purified oligonucleotides were then labeled with ³²P-αdATP using a Prime-It II labeling kit containing Exo (-) Klenow enzyme from Stratagene Inc. according to the manufacturer's protocol. The specific activity of all oligonucleotides was determined by scintillation counting.

The DNA-binding studies were performed as described above except that the agarose gel was not stained with ethidium bromide. Instead, following electrophoresis, the agarose gel was dried under vacuum and exposed to X-ray film for 4 h at room temperature prior to protein staining in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomassie Brilliant Blue R-250 (Bio-Rad Labs). Oligonucleotides and human LDL were present at 400,000 cpm and 40 µg protein per lane respectively.

5. Sonication of plasma lipoproteins

Solutions of plasma lipoproteins in phosphate-buffered saline containing 10 mM MgCl₂ were kept on ice and sonicated for various time periods ranging from 0 to 6 minutes in a Sonifier Model 350 sonicator (Branson Sonic Power Co.) at the following settings: duty cycle; 30%, pulsed, output control; level 2. Immediately following sonication, genomic DNA was added to the sonicated solutions, and the DNA-binding assay (see above) was started.

6. RT-PCR™ of Lipoprotein-bound RNA

Human liver RNA, complexed to human LDL or to human VLDL as described above, was subjected to agarose gel electrophoresis and extracted from the gel by solubilizing the gel for 20 min at 50°C in 3 times the gel volume of QX-1 buffer (Qiagen) and by twice adding an equivalent volume of phenol/chloroform (pH 4.0). RNA was precipitated by adding an

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equivalent volume of 100% isopropanol and freezing the mixture overnight at -80°C. RNA pellets were dissolved in 50 µl of DEPC-treated water. For each reaction, the dissolved RNA (3 µl) was transcribed in reverse into single-stranded DNA by adding 100 mM KCl, 10 mM Tris-HCl (pH 8.3), 5 mM MgCl₂, 2.5 µM primer (oligo d(T) or random hexamers), 1 U/µl RNase inhibitor, 1 mM each of dATP, dCTP, dTTP, and dGTP, and 2.5 U/µl of MuLV reverse transcriptase in a total reaction volume of 20 µl. The single-stranded DNA samples were then amplified in 100 mM KCl, 10 mM Tris-HCl (pH 8.3), 2 mM MgCl₂, 0.15 µM each of the forward and reverse ISRE primers (see Table 2), 1 mM each of dATP, dCTP, dTTP, and dGTP, and 2.5 U/100 µl of AmpliTaq DNA polymerase in a total reaction volume of 100 µl. DNA amplification was carried out in a thermocycler in 30 consecutive cycles of denaturing at 95°C for 60 sec, reannealing at 55°C for 60 sec, primer extension at 72°C for 120 sec, and a final extension at 72°C for 7 min. For each PCR reaction, 10 µl of the reaction mixture was analyzed by electrophoresis on a 1% agarose gel in TBE buffer (45 mM Tris-borate and 1 mM EDTA, pH 8.0) while maintaining a 100-V constant for 1 h. The PCR products were visualized by staining the gel with ethidium bromide.

7. DNA sequencing

DNA fragments obtained from the RT-PCR reactions were separated by electrophoresis on a 1% agarose gel and extracted from the gel by using a Qiagen gel extraction kit according to the manufacturer's protocol. DNA samples were analyzed on an Applied Biosystems Inc. model 373 automated DNA sequence apparatus after dye-terminator thermo cycle sequencing.

8. Cell culture and transfection assays.

Human skin fibroblasts were cultured in complete growth medium consisting of Dulbecco's modified Eagle's medium that was supplemented with 10% fetal bovine serum, 100 µg/ml each of streptomycin and penicillin at 37°C in an atmosphere of 5% CO₂ in a humidified incubator. Twenty-four hours before cell transfection, during exponential growth, the cultured cells were harvested by trypsinization, replated at a cell density of 1×10^6 cells in 35-mm culture dishes containing a glass coverslip, and cultured in complete growth medium. All transfection experiments were performed in triplicate as described.

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9. LipoFectin assay.

The pEGFP-N1 plasmid and LipoFectin were mixed together at a ratio of 1:4 (wt/wt) in 200 µl of serum-free medium and incubated for 15 min at room temperature. When the cells reached 40 to 60% confluence, they were transfected with a mixture of 5 µg of DNA and 20 µg of LipoFectin per 35-mm culture dish, each dish having been diluted in 1 ml of serum-free medium. Transfection was performed for 16 h at 37°C. Once transfection was achieved, the liposomes were removed from the culture dish by gentle washing and maintained in 2 ml of growth medium per 35-mm culture dish for 24 h at 37°C. Expression of GFP in the cells was determined by fluorescence microscopy

10. LDL assay.

The pEGFP-N1 plasmid and LDL were mixed together at a ratio of 1:10 (wt/wt) in 100 µl of serum-free medium containing 10 mM MgCl₂ and incubated for 15 min at 37°C. When the cells were 40 to 60% confluent, they were transfected for 16 h at 37°C with a mixture of 5 µg of DNA and 50 µg of LDL per 35-mm culture dish, each dish having been diluted in 1 ml of serum-free medium. Once transfection was achieved, the LDLs were removed by gentle washing and maintained in 2 ml of growth medium per 35-mm culture dish for 24 h at 37°C. At 24 h after transfection, the cells were washed with PBS and fixed in 2 ml of PBS containing 4% paraformaldehyde per 35-mm culture dish for 30 min. The coverslips were then removed from the culture dishes, washed with PBS, placed in an inverted orientation on glass slides, and examined by fluorescent microscopy to detect GFP.

11. *In vivo* reporter gene expression.

Two-month-old female Sprague-Dawley rats were anesthetized with a combination anesthetic (42.8 mg/ml ketamine, 8.6 mg/ml xylazine, and 1.4 mg/ml acepromazine), and a prebound complex of purified rat LDL and linearized pEGFP-N1 plasmid DNA was injected intravenously (into the femoral vein), subcutaneously, intraperitoneally, and into the pharyngeal, nasal, and rectal mucosae (100 µg of LDL protein and 5 µg of DNA in 100 µl of PBS containing 10 mM MgCl₂ per site). Control animals were injected with linearized pEGFP-N1 plasmid DNA in which the HCMV IE promoter sequence was interrupted only by digestion with restriction enzymes. 5 µg of DNA in 100 µl of PBS containing 10 mM MgCl₂ per site.

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After 2, 5, or 7 days, all the treated and control rats were sacrificed, their blood was collected by means of cardiac puncture, and the tissues were excised and immobilized in OCT by means of snap freezing over liquid nitrogen or by immediate freezing in liquid nitrogen. The immobilized tissue samples were sectioned on a cryomicrotome, and the sections (5–8 μ m thick) were fixed for 30 min in 4% paraformaldehyde and analyzed for expression of EGFP (green fluorescent protein) by fluorescent microscopy.

12. Fluorescent microscopy.

Microscopy was performed by using an Olympus Model BH-2 fluorescent microscope (Olympus, USA) equipped with a digital camera (Hamamatsu, Model C5810) and a color printer (Image Master, Toshiba). The filter set used was a standard fluorescein isothiocyanate (FITC) set (Chroma Technology, Brattleboro, VT, USA). The maximum excitation and emission wavelengths for this filter set were 485 nm (range 460–510 nm) and 540 nm (range 515–565 nm), respectively. Transfection efficiency was determined by calculating the average percentage of transduced cells of five different fields per 35-mm culture dish.

13. Detection of GFP.

Excised rat tissues were homogenized in 150 μ l of PBS in a dounce homogenizer placed on ice. The homogenized tissues were centrifuged for 3 min at $13,000 \times g$, and 50- μ l aliquots were withdrawn and used in an ELISA assay to detect GFP. First, serial dilutions (range 1:10 to 1:1,000) of all samples were made in PBS. ELISA plates (96 wells) were coated with the samples (three wells/sample) by incubating the plates at room temperature for 3 h. The plated samples were then washed three times with 200 μ l of $1 \times$ PBS containing 0.1% Tween 20 (PBST) and blocked with 200 μ l of PBST containing 1% bovine serum albumin (BSA) for 2 h at room temperature while shaking gently. The washing procedure was repeated with 200 μ l of PBST containing 0.1% BSA, and the plated samples were incubated with a 1:2,000 dilution of a recombinant GFP polyclonal antibody (IgG fraction, Clontech Inc., Palo Alto, CA) in PBST containing 0.1% BSA (50 μ l of diluted mixture per well) for 18 h at 4°C while shaking gently. The plated samples were washed and incubated with a 1:5000 dilution of HRP-conjugated goat anti-rabbit antibody (IgG fraction, Cappel, Durham, NC) in PBST containing 0.1% BSA for 1 h at room temperature while shaking gently. The washing procedure was repeated and was

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followed by a final wash with $1 \times$ PBS. GFP was detected after a 30-min incubation at room temperature in PBS containing σ -phenylenediamine as a chromogenic substrate.

EXAMPLE 2

BINDING OF HUMAN GENOMIC DNA TO HUMAN LDL

5 The binding of human genomic DNA (hg DNA) to human LDL has also been demonstrated. Each lane of the agarose gel contained hg DNA cut with *AluI* or *HindIII*. In addition, human VLDL and mouse LDL were run alongside the hg DNA.

10 Plasma lipoproteins were isolated from human or mouse blood according to the protocol described above. DNA-binding studies were performed using human genomic DNA digested with either *AluI* or *HindIII*. Following electrophoresis, the gel was stained for DNA with ethidium bromide prior to protein staining in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomassie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs).

15 Each lane contained 5 μ g human genomic DNA (hg DNA) cut with *AluI* or *HindIII*. In addition, human VLDL (10 μ g protein per lane) human LDL (35 μ g protein per lane) and mouse LDL (10 μ g protein per lane) were also analysed.

20 Bands in this study showed specific binding of digested human DNA fragments and human LDL by gel-shift electrophoresis. DNA fragment obtained by *AluI* or *HindIII* digestion of human genomic DNA are shown to migrate toward the anode with much slower mobility when preincubated with human LDL but not when incubated with human VLDL, human HDL, or mouse LDL. The complexed DNA/lipoprotein band are first visualized using DNA-binding ethidium bromide and photographed using transmitted ultra-violet light for activation of the
25 fluorescent dye. Lipoproteins were next visualized with CBB and photographed using transmitted visible light. The results shown in this figure indicate that aliquots of *AluI*- and *HindIII*-digested human genomic DNA fragments comigrate with human LDL and are therefore bound to human LDL.

30 While *AluI*, and *HindIII* were used to digest genomic DNA in the studies shown here, the inventors of the instant invention have also used *BamHI*, and *PvuI* for genomic DNA digest.

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It is understood by those of skill in the art that there are many known restriction enzymes. All of which are capable of genomic DNA digestion resulting in DNA that can be successfully bound to LDL. DNA digested with *AluI* yields DNA of very small size (200-700 nucleotides) which allows isolation of the slower migrating digested DNA bound to LDL from the unbound digested DNA using agarose gel electrophoresis. Digestion of genomic DNA with *HindIII* yields genomic DNA of greater average size (1000-7000 nucleotides) which reaches the upper size limit for separation by agarose gel electrophoresis (the technique used here), however there are other known DNA separation techniques which would work similarly to accomplish the goal of separating free DNA from DNA bound to LDL. The choice of which separation technique to use is dependent only on the size of the DNA fragments resulting after digestion. In principal, undigested genomic DNA would also work.

EXAMPLE 3

BINDING OF PLASMID DNA TO HUMAN LDL

Plasma LDL were isolated from human blood according to the protocol previously described in Example 1. DNA-binding studies were using DNA (pBluescript II KS, Stratagene Inc.) digested with *PvuI*. Following electrophoresis, the agarose gel was stained for DNA with ethidium bromide prior to protein staining in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomassie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs). The binding of plasmid DNA to human LDL was shown in a gel which contained contains 0.5 µg molecular size DNA marker (Lane 1); 2 µg pKS DNA cut with *PvuI* (Lanes 2-4); 35 µg human LDL (Lane 3) and 70 µg human LDL protein (Lane 4).

Results of the electrophoretogram illustrated specific binding of *PvuI* digested plasmid DNA (pBluescript II KS, Stratagene Inc.) and human LDL. Increased amounts of human LDL also caused an increase of DNA shifted to the LDL location and a decrease of the free *PvuI* digested DNA band. Co-migration of the *PvuI* digested DNA and human LDL are proof of a physical complex composed of LDL and DNA.

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EXAMPLE 4
BINDING OF CMV PROMOTER-REGULATORY
SEQUENCES TO HUMAN LDL

Plasma lipoproteins were isolated from human or mouse blood according to the protocol previously described in Example 1. DNA-binding studies were performed using plasmid DNA (either pBluescript II KS or pBKCMV, Stratagene Inc.) digested with *Bam*HI. Following electrophoresis the agarose gel was stained for DNA with ethidium bromide prior to protein staining in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomassie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs). Loading quantities per lane were as follows:

| | |
|--------------|-------------------------|
| plasmid DNA: | 1 μ g DNA/lane |
| human VLDL | 35 μ g protein/lane |
| human LDL | 35 μ g protein/lane |
| mouse VLDL: | 8 μ g protein/lane |
| mouse LDL: | 35 μ g protein/lane |

This study used *Bam*HI cut pIGS, *Bam*HI cut pBKCMV, human VLDL, human LDL, mouse VLDL and mouse LDL.

A comparison of human LDL complexed with *Bam*HI linearized plasmids, pBluescript II KS or pBKCMV. The inventors' results illustrated that specific binding of *Bam*HI linearized plasmid DNA and human LDL occurs, but these *Bam*HI linearized plasmids do not complex with either human VLDL, mouse VLDL or mouse LDL under the conditions previously described in the DNA-binding protocol (Example 2). Further, enhanced binding of human LDL and the *Bam*HI linearized plasmid pBKCMV DNA which contains the cytomegalovirus promoter region SEQ ID NO:225 (Table 2) was observed as compared to the *Bam*HI linearized plasmid pBluescript II KS DNA that does not contain the cytomegalovirus promoter region (lane 3). Because binding of DNA by LDL is enhanced in the presence of the CMV promoter, it is possible that LDL binds specifically to the CMV promoter sequence (SEQ ID NO:225, see Table 2).

Aliquots containing approximately 8 μ g mouse VLDL protein were used in each DNA-binding assay mixtures resolved in lanes 4 and 9 as compared to 35 μ g of total protein of all

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other lipoproteins (lanes 2, 3, 5, 7, 8, and 10). Due to the low physiological concentration of VLDL in mouse plasma and the limited loading capacity of the gel, it was not possible to load 35 µg of mouse VLDL protein per lane. Therefore, this study does not allow for a quantitative comparison of the plasmid DNA-binding capacity of mouse VLDL vs. human VLDL, human LDL, and mouse LDL.

TABLE 2

Nucleotide Sequence of the Promoter Region (1300-1900) of the Human Cytomegalovirus
SEQ ID NO:225

| | | | | |
|-------------------|-------------------|------------|-------------------|-------------------|
| GGATCTGACG | GTTCACTAAA | CCAGCTCTGC | TTATATAGAC | CTCCCACCGT |
| ACACGCCTAC | CGCCCATTTG | CGTCAATGGG | GCGGAGTTGT | TACGACATTT |
| TGGAAAGTCC | CGTTGATTTT | GGTGCCAAAA | CAAACCTCCAT | TGACGTCAAT |
| <u>GGGGTGGAGA</u> | CTTGGAAATC | CCCGTGAGTC | AAACCGCTAT | CCACGCCCAT |
| <u>TGATGTACTG</u> | <u>CCAAAACCGC</u> | ATCACCATGG | TAATAGCGAT | GACTAATACG |
| <u>TAGATGTACT</u> | <u>GCCAAGTAGG</u> | AAAGTCCCAT | AAGGTCATGT | ACTGGGCATA |
| ATGCCAGGCG | GGCCATTTAC | CGTCATTGAC | GTCAATAGGG | <u>GGCGTACTTG</u> |
| GCATATGATA | CACTTGATGT | ACTGCCAAGT | GGGCAGTTTA | CCGTAAATAC |
| TCCACCCATT | GACGTCAATG | GAAAGTCCCT | ATTGGCGTTA | CTATGGGAAC |
| ATACGTCATT | ATTGACGTCA | ATGGGCGGGG | <u>GTCGTTGGGC</u> | GGTCAGCCAG |
| GCGGGCCATT | <u>TACCGTAAGT</u> | TATGTAACGC | GGAACCTCCAT | ATATGGGCTA |
| TGAACTAATG | <u>ACCCCGTAAT</u> | TGATTACTAT | TAATAACTA | |

Major repeat regions are indicate in bold and underlined.

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EXAMPLE 5
BINDING OF SRE, E/C, FAS, AND ISRE
DEOXYNUCLEOTIDE SEQUENCES TO HUMAN LDL

Plasma lipoproteins were isolated from human or mouse blood according to the protocol previously described in Example 1. DNA-binding studies were performed using the synthetic oligonucleotides: SRE, E/C, and FAS (see Table 3 for nucleotide sequences).

TABLE 3
Deoxyribonucleic Acid Sequences of Synthetic Oligonucleotides
used in Binding Studies with LDL

| SEQ ID NO | Oligo Name | Sequence (5'-3') |
|-----------|------------|-------------------------------------|
| 226 | SRE-2A | GATCCAAATCACCCACTGCAACTCCTCCCCCTGCG |
| 227 | E/C-1A | GATCCATCCAATTGGGCAATCAGGAG |
| 228 | FAS- 1A | GATCCGGTCTCCAATTGG |
| 229 | ISRE- 1A | GATCCTCGGGAAAGGGAAACCGAAACTGAAGCCG |

DNA-binding studies were performed according to the previously described DNA-binding protocol (Example 2). Following electrophoresis, the agarose gel was stained for DNA with ethidium bromide prior to protein staining in a solution containing 50% V/V ethanol, 10% V/V acetic acid, and 0.25% Coomassie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs). Oligonucleotides were present at 1 µg DNA per lane. Lanes containing human LDL contained 35 µg protein per lane and lanes containing mouse LDL contained 15 µg protein per lane.

The data generated showed the complexed synthetic, double-stranded oligonucleotide fragments and human LDL. The results strongly support that human LDL binds to these DNA sequences in a highly specific fashion. The synthetic oligonucleotides SRE-2A, E/C-1A, FAS-1A, and ISRE-1A (Table 3, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, and SEQ ID NO:229 respectively) bind to human LDL but do not bind to mouse LDL. DNA binding to human LDL is illustrated by the appearance of a fraction of slower mobility DNA that comigrates with human LDL.

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In another embodiment of this same study, binding was determined using radioisotope labeling of the deoxynucleotide sequences as described in Example 1. The results from these DNA-binding studies show that human LDL binds to the synthetic oligonucleotides SRE-2A, E/C-1A, FAS-1A, and ISRE-1A (Table 3, SEQ ID NO:226; SEQ ID NO:227; SEQ ID NO:228; SEQ ID NO:229) in a highly specific fashion. DNA binding to human LDL is illustrated by the appearance of a fraction of slower mobility DNA that comigrates with human LDL. The binding affinity of the different synthetic oligonucleotides for human LDL can be determined by kinetic binding studies using quantitative autoradiography well known to those of skill in the art.

EXAMPLE 6

BINDING OF VARIOUS NUCLEOTIDE SEQUENCES TO THE LDL ISOLATED FROM VARIOUS SPECIES

Plasma lipoproteins were isolated from human, mouse, rat, or baboon blood according to the protocol previously described in Example 1. DNA-binding studies were performed according to the previously described DNA-binding protocol using the synthetic oligonucleotides: SRE, E/C, and FAS (see Table 3 for nucleotide sequences), genomic DNA, or plasmid DNA containing the CMV promoter. A summary of the binding studies of the instant invention are illustrated in Tables 4A and 4B, below. Table 4A illustrates the binding of human, mouse, rat and baboon LDL to various forms and sources of DNA, and Table 4B illustrates the DNA/LDL complexes made thus far.

TABLE 4A

Binding of Human, Mouse, Rat and Baboon LDL to Various Forms of DNA

| DNA | human LDL | mouse LDL | rat LDL | baboon LDL |
|--------|-----------|-----------|---------|------------|
| hg DNA | YES | NO | YES | YES |
| mg DNA | N.D. | N.D. | YES | N.D. |

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| | | | | |
|--------|------|------|------|------|
| rg DNA | N.D. | N.D. | YES | N.D. |
| bg DNA | N.D. | N.D. | N.D. | YES |
| CMV | YES | NO | YES | YES |
| SRE | YES | NO | N.D. | NO |
| E/C | YES | NO | N.D. | NO |
| FAS | YES | NO | N.D. | NO |

hg = human genomic DNA (digested with either *AluI* or *HindIII*, mg = mouse genomic DNA digested with either *AluI* or *HindIII*, rg = rat genomic DNA digested with either *AluI* or *HindIII*, and bg = baboon genomic DNA digested with either *AluI* or *HindIII*

Yes = binding, NO = no binding, N.D. = binding not determined

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TABLE 4B
Specific LDL/DNA Complexes That Have Been Made

| DNA | DNA Digested With | LDL |
|----------------|--------------------------|------------|
| human genomic | <i>AluI</i> | human |
| human genomic | <i>HindIII</i> | human |
| human genomic | <i>Bam</i> HI | human |
| human genomic | <i>Pvu</i> I | human |
| human genomic | <i>AluI</i> | rat |
| human genomic | <i>HindIII</i> | rat |
| human genomic | <i>Bam</i> HI | rat |
| human genomic | <i>Pvu</i> I | rat |
| human genomic | <i>AluI</i> | baboon |
| human genomic | <i>HindIII</i> | baboon |
| human genomic | <i>Bam</i> HI | baboon |
| human genomic | <i>Pvu</i> I | baboon |
| mouse genomic | <i>AluI</i> | rat |
| mouse genomic | <i>HindIII</i> | rat |
| rat genomic | <i>AluI</i> | rat |
| rat genomic | <i>HindIII</i> | rat |
| baboon genomic | <i>AluI</i> | baboon |
| baboon genomic | <i>HindIII</i> | baboon |
| pBSKS | <i>Pvu</i> I | human |
| pBSKS | <i>Bam</i> HI | human |
| pBKCMV | <i>Bam</i> HI | human |
| pBKCMV | <i>Bam</i> HI | rat |

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TABLE 4B (cont'd)

| DNA | DNA Digested With | LDL |
|---------------|-------------------|--------|
| pBKCMV | <i>Bam</i> HI | baboon |
| SRE-2A oligo | none | human |
| SEQ ID NO:226 | | |
| E/C-1A oligo | none | human |
| SEQ ID NO:227 | | |
| FAS-1A oligo | none | human |
| SEQ ID NO:228 | | |
| ISRE-1A oligo | none | human |
| SEQ ID NO:229 | | |

EXAMPLE 7

DETECTION OF LDL-BOUND DNA IN HUMAN BLOOD

5 Plasma lipoproteins are isolated from human blood according to the protocol previously described in Example 1. 6X Sample loading buffer (30% glycerol, 0.25% Xylene cyanole FF, 0.25% bromophenol blue) is added to the samples in a 1:5 V/V ratio. Samples are underloaded into 30 μ l wells at the cathode edge of an 0.8% agarose gel in Tris-Acetate buffer (pH 7.85) and electrophoresis is accomplished using 100 Volt constant until the negatively charged tracking

10 dye migrates at least 50% of the distance from the loading well to the anodic edge of the gel. Following electrophoresis, is stained for DNA with ethidium bromide prior to protein staining in a solution containing 50% V/V ethanol, 10% V/V acetic add, and 0.25% Coomassie Brilliant Blue R-250 (CBB R-250, Bio-Rad Labs). If no DNA is detected by ethidium bromide staining, the agarose gel is subjected to Southern blot analysis using a labeled DNA probe. The DNA is

15 labeled with a radioactive isotope (*e.g.*, ^{32}P), a non-radioactive tag (DIG) or with any other standard DNA-labeling method known to one of skill in the art. Randomly synthesized, short oligonucleotides are used as the probe to detect, in a general fashion, whether or not DNA is bound to the isolated LDL. Controls include lanes containing known quantities of DNA, lanes

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containing purified LDL digested with DNase I, and LDL bound to DNA made by mixing purified LDL and DNA according to the method described in Example 2.

LDL isolated from humans with cancer and subjected to the above protocol will have detectable DNA bound to the LDL in quantities greater than the amount of DNA bound to LDL isolated from humans without cancer.

EXAMPLE 8

DETECTION OF SPECIFIC TYPES OF CANCERS WITH SEQUENCE SPECIFIC DNA PROBES

Not only is it possible to identify the presence or absence of cancer in a living body using the invention technique (as described in Example 14 above), it is also possible to identify specific cancer types by using sequence specific DNA probes. For example, LDL-bound DNA isolated from a patient with colon cancer will have a different DNA sequence than the LDL-bound DNA isolated from a patient with a different cancer type, for example, breast cancer. Different DNA sequences bound to the LDL isolated from different cancer patients is determined by first isolating LDL from the blood of a person with an independently identified and known cancer type, using the protocol in Example 1. This isolated LDL is then digested with various non-specific proteases to remove the LDL while retaining the DNA. This DNA is then sequenced using standard sequencing techniques. A list of the DNA sequences along with the type of cancer it is associated with is made. This list is then used to synthesize probes that can differentiate among the various types of cancer. These probes are used in screening of a patient with an unknown cancer type, or in the early detection of metastatic cancer, or as a general early screening technique for the presence or absence of specific cancer types.

EXAMPLE 9

METHODS FOR THE DETERMINATION OF METASTATIC GENE TRANSFER VIA LIPOPROTEINS AS NATIVE VECTORS

5 In order to determine the sequence of polynucleotides bound to endogenous LDL, plasma LDL and other apoB-containing lipoproteins are captured using a monoclonal antibody to a specific apoB epitope such as 2G8 which is immobilized on an inert, hydrophilic and highly porous polymer microbead. The LDL-DNA complex is then isolated by elution using affinity chromatography technology. DNA is further purified from the isolated LDL/DNA complex using standard DNA purification methodology such as phenol/chloroform extraction
10 followed by ethanol precipitation. Alternatively, purified DNA is isolated from the affinity column using elution conditions that disrupt protein/DNA complexes but not protein/protein complexes (*i.e.*, antibody/LDL complex). The polynucleotide sequences are determined using the SRE, E/C, FAS, and ISRE-1A oligonucleotides (SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, and SEQ ID NO:229, respectively) in a standard PCR™ methodology in order to
15 amplify polynucleotides with unknown sequences. The amplified PCR™ products (*i.e.*, polynucleotides) are then isolated by agarose gel electrophoresis and subsequent DNA sequencing techniques well known to the art.

20 Alternatively, identification of polynucleotide sequences that are bound to endogenous human LDL is *via* the specific binding of LDL to a plastic matrix such as a 96 well ELISA (enzyme linked immunosorbant assay) plates coated with specific antibodies that bind to human LDL. In this embodiment, freshly isolated plasma containing endogenous lipoproteins is used to bind to the anti-human LDL antibodies using standard ELISA procedures lipoproteins to the art. The presence and specific sequence of polynucleotides prebound to the endogenous LDL in
25 each is determined by PCR™ technology.

Because many varying and different embodiments may be made within the scope of the inventive concept herein taught, and because many modifications may be made in the embodiments herein detailed in accordance with the descriptive requirement of the law, it is to

be understood that the details herein are to be interpreted as illustrative and not in a limiting sense.

EXAMPLE 10

LOW-DENSITY LIPOPROTEIN INTERACTS WITH HUMAN CYTOMEGALOVIRUS GENOMIC DNA

DNA binding experiments with purified plasma lipoprotein fractions and human genomic DNA as well as several different plasmids indicate that purified LDL binds to human genomic DNA digested with different restriction enzymes (Alu I and Hind III).

Purified LDL also bound to several different plasmids but its binding affinity for plasmid DNA containing the HCMV IE promotor region was significantly higher. It was shown that the binding of both LDL and VLDL to the HCMV IE promotor region and SRE, MSRE, ISRE, MISRE, E/C, FAS, and MFAS oligonucleotides. The E/C oligonucleotide was used in these DNA binding studies because this oligonucleotide contains both a binding site for members of the C/EBP transcription factor family, which are involved in the regulation of differentiation-dependent adipocyte gene expression, as well as an overlapping E-box motif which is generally recognized by the eukaryotic basic helix-loop-helix (b-HLH) transcriptional regulators. LDL clearly have a greater affinity for all of the oligonucleotides tested than do VLDL. This is most likely due to interference with protein-DNA interaction caused by either the presence of other apolipoproteins on the surface of VLDL or an increased net charge as a result of the increased lipid content of VLDL.

The sequence specificity is illustrated by the fact that both LDL and VLDL show a decreased binding affinity for the mutated versions of the ISRE and FAS oligos (MISRE and MFAS respectively). In contrast, LDL showed an increased binding affinity for the mutated version of the SRE oligo (MSRE). It is possible that this mutated SRE sequence may be a better ligand for the putative DNA binding region of apo B present on LDL. The binding of both VLDL and LDL to the E/C oligonucleotide is not surprising since this oligo contains the

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E-box motif which is a known binding site for b-HLH proteins and similar b-HLH regions have been identified in apoB present on VLDL and LDL.

5 The affinity for the HCMV IE promotor is not immediately obvious since careful analysis does not reveal an exact copy of either a SRE, ISRE, FAS, or E/C sequence. However, the HCMV IE promotor region contains regulatory elements that are generally recognized by a large number of eukaryotic DNA-binding proteins, including a variety of different families of transcription factors, and it may therefore be possible that the identified b-HLH regions of apoB possess similar DNA binding properties.

10 Another possibility is that other yet unidentified regions of apoB are involved in the binding to the HCMV IE promotor region. The fact that HDL in contrast to VLDL and LDL do not bind to any of the oligos tested suggests that the DNA binding results from the specific interaction with apo B. These data support the hypothesis that apo B contains DNA binding domains which show homology with the DNA binding domains of SREBP-1, SREBP-2, ADD-1, and ISGF3 γ and that apo B containing lipoproteins therefore bind to specific nucleotide sequences similar to those bound by these known DNA binding proteins.

20 Recent reports suggest a possible causal relationship between human cytomegalovirus (HCMV) and the development of atherosclerosis in humans. These reports together with data presented herein, which show that human LDL binds strongly to HCMV IE promotor sequences, led the inventors to investigate whether plasma LDL may play a role in the pathogenesis of HCMV induced atherosclerosis.

25 To test this hypothesis, the inventors looked for HCMV DNA sequences in the purified plasma LDL fraction of human subjects who tested seropositive for HCMV by polymerase chain reaction (PCR). The results of these studies show that a PCR product of the expected size (170 bp) could be detected with both primer sets (MTR2 and IE) in the purified plasma LDL fraction of HCMV seropositive subjects. However, this 170 bp DNA fragment could not be
30 detected in the plasma samples of these subjects (lanes 6-8). These data suggest that the use of purified plasma LDL fractions for detection of CMV nucleic acid sequences by PCR techniques

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is more sensitive than when whole plasma samples are used. Furthermore, the increased yield of PCR products of the purified plasma LDL fractions strongly suggest that HCMV DNA is predominantly associated with LDL within the plasma pool of HCMV seropositive subjects.

EXAMPLE 11

LOW-DENSITY LIPOPROTEIN AS A NATURAL GENE TRANSFER VECTOR

The discovery of the nucleic acid-binding properties apo B-100 suggested that lipoproteins containing apoB100, as naturally occurring liposomes, may function as gene transfer agents. By using highly purified low-density lipoprotein as such an agent, the inventors were able to transfect cultured human skin fibroblasts *in vitro* and to express a green fluorescent protein reporter gene *in vivo*. The gene transfer mediated by low-density lipoprotein was more efficient than that mediated by LipoFectin. Low-density lipoprotein also did not exhibit any toxicity, immunogenicity, or serum inhibition.

1. DNA-binding

In the Examples above, it was shown that highly purified human LDL binds to nucleic acids in a specific fashion. In order to establish whether rat lipoproteins can bind nucleic acids in a similar fashion, DNA-binding experiments with different rat lipoprotein fractions were performed. A gel shift assay of linearized pBluescript KS and pBKCMV plasmid DNA and purified rat VLDL, LDL, and HDL fractions was performed. The data clearly demonstrate that the binding of nucleic acids is specific to the purified LDL fraction.

The binding of LDL to DNA is exhibited by the retarded electrophoretic migration of DNA in agarose gel that is caused by the formation of complexes of higher molecular weight. In contrast, purified fractions of VLDL and HDL did not bind any of the DNA samples tested. The fact that purified HDL did not bind DNA was expected, since endogenous HDL does not contain apo B-100. Surprisingly, there was no apparent binding of DNA to apo B-100-containing VLDL. It is possible that the DNA-binding assay, which employs ethidium bromide staining to detect DNA, lacks sensitivity or that VLDL does not bind to DNA under the conditions of the DNA-binding assay. Another explanation could be a difference in the

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conformation of apo B-100 present on LDL as opposed to VLDL because of a difference in the lipid composition and protein content of the two lipoprotein fractions.

2. *In vitro* cell transfection studies.

Based on the findings of the DNA-binding assay, transfection studies were performed using a prebound complex of LDL and plasmid DNA that contained a reporter gene that encodes GFP.

The data generated illustrated the successful transfection of how human skin fibroblasts with LDL and pEGFP-N1 plasmid DNA. The transfection process was monitored by expression of the GFP encoding gene and is driven by the HCMV IE promoter. In addition to fluorescent microscopic analysis, expression of GFP was confirmed by a qualitative ELISA using a primary antibody against recombinant GFP and an HRP-conjugated secondary antibody with σ -phenylenediamine as a chromogenic substrate.

Human skin fibroblasts transfected with LDL exhibited a significantly lower intensity of green fluorescence than did cells transfected with LipoFectin, indicating that the level of GFP expression was lower in these LDL-transfected cells. When the percentage of positively transfected cells were compared, however, transfection with LDL yielded a higher percentage of transfected cells than did transfection with LipoFectin (20 to 30% and 60 to 70%, respectively). In addition, LipoFectin-mediated transfection resulted in green fluorescence in the cell cytoplasm and in the nuclei, whereas LDL-mediated transfection resulted in green fluorescence predominantly in the cytoplasm.

Transfection assays in which LDL concentrations were as high as 250 g/ml of LDL protein produced no detectable effects on the confluence and viability of the cell cultures, whereas LipoFectin concentrations of 20 g/ml resulted in significant loss of cell viability. Control cells that were transfected with linearized pEGFP-N1 plasmid DNA only exhibited no fluorescence.

3. *In vivo* reporter gene expression.

To evaluate whether LDL could be used as a vehicle for *in vivo* gene delivery, a prebound rat LDL-pEGFP-N1 complex was administered to 2-month-old female Sprague-Dawley rats. Cryosections of the liver and heart tissues of the treated animals that had been excised 2 days after the LDL-pEGFP-N1 complex showed significant levels of green fluorescence indicative of EGFP expression as determined by fluorescent microscopy.

The expression of GFP in the different tissues was confirmed by a qualitative ELISA using a primary antibody against recombinant GFP and an HRP-conjugated secondary antibody with σ -phenylenediamine as a chromogenic substrate. In contrast, only low levels of autofluorescence were observed in the cryosectioned tissues obtained from the control animals treated solely with linearized pEGFP-N1 DNA. These data demonstrate that purified LDL can be used in a prebound complex with DNA as an *in vivo* gene delivery system.

* * *

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims

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The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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- U.S. Patent No. 4,497,796
- U.S. Patent No. 4,663,292
- U.S. Patent No. 4,868,116
- 10 U.S. Patent No. 4,885,248
- U.S. Patent No. 4,904,582
- U.S. Patent No. 5,023,243
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- 15 U.S. Patent No. 5,168,062
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- 25 U.S. Patent No. 5,523,222
- U.S. Patent No. 5,547,932
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- U.S. Patent No. 5,578,475
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(iii) NUMBER OF SEQUENCES: 229

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(v) CURRENT APPLICATION DATA:

APPLICATION NUMBER: US 98/11927

(vi) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 09/079,030
(B) FILING DATE: 14-MAY-1998

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(vi) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: US 08/874,807
 (B) FILING DATE: 13-JUN-1997

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4536 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Glu | Glu | Met | Leu | Glu | Asn | Val | Ser | Leu | Val | Cys | Pro | Lys | Asp | Ala | 1 | 5 | 10 | 15 |
| Thr | Arg | Phe | Lys | His | Leu | Arg | Lys | Tyr | Thr | Tyr | Asn | Tyr | Glu | Ala | Glu | 20 | 25 | 30 | |
| Ser | Ser | Ser | Gly | Val | Pro | Gly | Thr | Ala | Asp | Ser | Arg | Ser | Ala | Thr | Arg | 35 | 40 | 45 | |
| Ile | Asn | Cys | Lys | Val | Glu | Leu | Glu | Val | Pro | Gln | Leu | Cys | Ser | Phe | Ile | 50 | 55 | 60 | |
| Leu | Lys | Thr | Ser | Gln | Cys | Thr | Leu | Lys | Glu | Val | Tyr | Gly | Phe | Asn | Pro | 65 | 70 | 75 | 80 |
| Glu | Gly | Lys | Ala | Leu | Leu | Lys | Lys | Thr | Lys | Asn | Ser | Glu | Glu | Phe | Ala | 85 | 90 | 95 | |
| Ala | Ala | Met | Ser | Arg | Tyr | Glu | Leu | Lys | Leu | Ala | Ile | Pro | Glu | Gly | Lys | 100 | 105 | 110 | |
| Gln | Val | Phe | Leu | Tyr | Pro | Glu | Lys | Asp | Glu | Pro | Thr | Tyr | Ile | Leu | Asn | 115 | 120 | 125 | |
| Ile | Lys | Arg | Gly | Ile | Ile | Ser | Ala | Leu | Leu | Val | Pro | Pro | Glu | Thr | Glu | 130 | 135 | 140 | |
| Glu | Ala | Lys | Gln | Val | Leu | Phe | Leu | Asp | Thr | Val | Tyr | Gly | Asn | Cys | Ser | 145 | 150 | 155 | 160 |
| Thr | His | Phe | Thr | Val | Lys | Thr | Arg | Lys | Gly | Asn | Val | Ala | Thr | Glu | Ile | 165 | 170 | 175 | |
| Ser | Thr | Glu | Arg | Asp | Leu | Gly | Gln | Cys | Asp | Arg | Phe | Lys | Pro | Ile | Arg | 180 | 185 | 190 | |
| Thr | Gly | Ile | Ser | Pro | Leu | Ala | Leu | Ile | Lys | Gly | Met | Thr | Arg | Pro | Leu | 195 | 200 | 205 | |

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Ser Thr Leu Ile Ser Ser Ser Gln Ser Cys Gln Tyr Thr Leu Asp Ala
 210 215 220
 Lys Arg Lys His Val Ala Glu Ala Ile Cys Lys Glu Gln His Leu Phe
 225 230 235 240
 Leu Pro Phe Ser Tyr Asn Asn Lys Tyr Gly Met Val Ala Gln Val Thr
 245 250 255
 Gln Thr Leu Lys Leu Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe Phe
 260 265 270
 Gly Glu Gly Thr Lys Lys Met Gly Leu Ala Phe Glu Ser Thr Lys Ser
 275 280 285
 Thr Ser Pro Pro Lys Gln Ala Glu Ala Val Leu Lys Thr Leu Gln Glu
 290 295 300
 Leu Lys Lys Leu Thr Ile Ser Glu Gln Asn Ile Gln Arg Ala Asn Leu
 305 310 315 320
 Phe Asn Lys Leu Val Thr Glu Leu Arg Gly Leu Ser Asp Glu Ala Val
 325 330 335
 Thr Ser Leu Leu Pro Gln Leu Ile Glu Val Ser Ser Pro Ile Thr Leu
 340 345 350
 Gln Ala Leu Val Gln Cys Gly Gln Pro Gln Cys Ser Thr His Ile Leu
 355 360 365
 Gln Trp Leu Lys Arg Val His Ala Asn Pro Leu Leu Ile Asp Val Val
 370 375 380
 Thr Tyr Leu Val Ala Leu Ile Pro Glu Pro Ser Ala Gln Gln Leu Arg
 385 390 395 400
 Glu Ile Phe Asn Met Ala Arg Asp Gln Arg Ser Arg Ala Thr Leu Tyr
 405 410 415
 Ala Leu Ser His Ala Val Asn Asn Tyr His Lys Thr Asn Pro Thr Gly
 420 425 430
 Thr Gln Glu Leu Leu Asp Ile Ala Asn Tyr Leu Met Glu Gln Ile Gln
 435 440 445
 Asp Asp Cys Thr Gly Asp Glu Asp Tyr Thr Tyr Leu Ile Leu Arg Val
 450 455 460
 Ile Gly Asn Met Gly Gln Thr Met Glu Gln Leu Thr Pro Glu Leu Lys
 465 470 475 480
 Ser Ser Ile Leu Lys Cys Val Gln Ser Thr Lys Pro Ser Leu Met Ile
 485 490 495

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Gln Lys Ala Ala Ile Gln Ala Leu Arg Lys Met Glu Pro Lys Asp Lys
 500 505 510

Asp Gln Glu Val Leu Leu Gln Thr Phe Leu Asp Asp Ala Ser Pro Gly
 515 520 525

Asp Lys Arg Leu Ala Ala Tyr Leu Met Leu Met Arg Ser Pro Ser Gln
 530 535 540

Ala Asp Ile Asn Lys Ile Val Gln Ile Leu Pro Trp Glu Gln Asn Glu
 545 550 555 560

Gln Val Lys Asn Phe Val Ala Ser His Ile Ala Asn Ile Leu Asn Ser
 565 570 575

Glu Glu Leu Asp Ile Gln Asp Leu Lys Lys Leu Val Lys Glu Ala Leu
 580 585 590

Lys Glu Ser Gln Leu Pro Thr Val Met Asp Phe Arg Lys Phe Ser Arg
 595 600 605

Asn Tyr Gln Leu Tyr Lys Ser Val Ser Leu Pro Ser Leu Asp Pro Ala
 610 615 620

Ser Ala Lys Ile Glu Gly Asn Leu Ile Phe Asp Pro Asn Asn Tyr Leu
 625 630 635 640

Pro Lys Glu Ser Met Leu Lys Thr Thr Leu Thr Ala Phe Gly Phe Ala
 645 650 655

Ser Ala Asp Leu Ile Glu Ile Gly Leu Glu Gly Lys Gly Phe Glu Pro
 660 665 670

Thr Leu Glu Ala Leu Phe Gly Lys Gln Gly Phe Phe Pro Asp Ser Val
 675 680 685

Asn Lys Ala Leu Tyr Trp Val Asn Gly Gln Val Pro Asp Gly Val Ser
 690 695 700

Lys Val Leu Val Asp His Phe Gly Tyr Thr Lys Asp Asp Lys His Glu
 705 710 715 720

Gln Asp Met Val Asn Gly Ile Met Leu Ser Val Glu Lys Leu Ile Lys
 725 730 735

Asp Leu Lys Ser Lys Glu Val Pro Glu Ala Arg Ala Tyr Leu Arg Ile
 740 745 750

Leu Gly Glu Glu Leu Gly Phe Ala Ser Leu His Asp Leu Gln Leu Leu
 755 760 765

Gly Lys Leu Leu Leu Met Gly Ala Arg Thr Leu Gln Gly Ile Pro Gln
 770 775 780

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|
| Met | Ile | Gly | Glu | Val | Ile | Arg | Lys | Gly | Ser | Lys | Asn | Asp | Phe | Phe | Leu | 785 | 790 | 795 | 800 |
| His | Tyr | Ile | Phe | Met | Glu | Asn | Ala | Phe | Glu | Leu | Pro | Thr | Gly | Ala | Gly | 805 | 810 | 815 | |
| Leu | Gln | Leu | Gln | Ile | Ser | Ser | Ser | Gly | Val | Ile | Ala | Pro | Gly | Ala | Lys | 820 | 825 | 830 | |
| Ala | Gly | Val | Lys | Leu | Glu | Val | Ala | Asn | Met | Gln | Ala | Glu | Leu | Val | Ala | 835 | 840 | 845 | |
| Lys | Pro | Ser | Val | Ser | Val | Glu | Phe | Val | Thr | Asn | Met | Gly | Ile | Ile | Ile | 850 | 855 | 860 | |
| Pro | Asp | Phe | Ala | Arg | Ser | Gly | Val | Gln | Met | Asn | Thr | Asn | Phe | Phe | His | 865 | 870 | 875 | 880 |
| Glu | Ser | Gly | Leu | Glu | Ala | His | Val | Ala | Leu | Lys | Ala | Gly | Lys | Leu | Lys | 885 | 890 | 895 | |
| Phe | Ile | Ile | Pro | Ser | Pro | Lys | Arg | Pro | Val | Lys | Leu | Leu | Ser | Gly | Gly | 900 | 905 | 910 | |
| Asn | Thr | Leu | His | Leu | Val | Ser | Thr | Thr | Lys | Thr | Glu | Val | Ile | Pro | Pro | 915 | 920 | 925 | |
| Leu | Ile | Glu | Asn | Arg | Gln | Ser | Trp | Ser | Val | Cys | Lys | Gln | Val | Phe | Pro | 930 | 935 | 940 | |
| Gly | Leu | Asn | Tyr | Cys | Thr | Ser | Gly | Ala | Tyr | Ser | Asn | Ala | Ser | Ser | Thr | 945 | 950 | 955 | 960 |
| Asp | Ser | Ala | Ser | Tyr | Tyr | Pro | Leu | Thr | Gly | Asp | Thr | Arg | Leu | Glu | Leu | 965 | 970 | 975 | |
| Glu | Leu | Arg | Pro | Thr | Gly | Glu | Ile | Glu | Gln | Tyr | Ser | Val | Ser | Ala | Thr | 980 | 985 | 990 | |
| Tyr | Glu | Leu | Gln | Arg | Glu | Asp | Arg | Ala | Leu | Val | Asp | Thr | Leu | Lys | Phe | 995 | 1000 | 1005 | |
| Val | Thr | Gln | Ala | Glu | Gly | Ala | Lys | Gln | Thr | Glu | Ala | Thr | Met | Thr | Phe | 1010 | 1015 | 1020 | |
| Lys | Tyr | Asn | Arg | Gln | Ser | Met | Thr | Leu | Ser | Ser | Glu | Val | Gln | Ile | Pro | 1025 | 1030 | 1035 | 1040 |
| Asp | Phe | Asp | Val | Asp | Leu | Gly | Thr | Ile | Leu | Arg | Val | Asn | Asp | Glu | Ser | 1045 | 1050 | 1055 | |
| Thr | Glu | Gly | Lys | Thr | Ser | Tyr | Arg | Leu | Thr | Leu | Asp | Ile | Gln | Asn | Lys | 1060 | 1065 | 1070 | |

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Lys Ile Thr Glu Val Ala Leu Met Gly His Leu Ser Cys Asp Thr Lys
 1075 1080 1085
 Glu Glu Arg Lys Ile Lys Gly Val Ile Ser Ile Pro Arg Leu Gln Ala
 1090 1095 1100
 Glu Ala Arg Ser Glu Ile Leu Ala His Trp Ser Pro Ala Lys Leu Leu
 1105 1110 1115 1120
 Leu Gln Met Asp Ser Ser Ala Thr Ala Tyr Gly Ser Thr Val Ser Lys
 1125 1130 1135
 Arg Val Ala Trp His Tyr Asp Glu Glu Lys Ile Glu Phe Glu Trp Asn
 1140 1145 1150
 Thr Gly Thr Asn Val Asp Thr Lys Lys Met Thr Ser Asn Phe Pro Val
 1155 1160 1165
 Asp Leu Ser Asp Tyr Pro Lys Ser Leu His Met Tyr Ala Asn Arg Leu
 1170 1175 1180
 Leu Asp His Arg Val Pro Glu Thr Asp Met Thr Phe Arg His Val Gly
 1185 1190 1195 1200
 Ser Lys Leu Ile Val Ala Met Ser Ser Trp Leu Gln Lys Ala Ser Gly
 1205 1210 1215
 Ser Leu Pro Tyr Thr Gln Thr Leu Gln Asp His Leu Asn Ser Leu Lys
 1220 1225 1230
 Glu Phe Asn Leu Gln Asn Met Gly Leu Pro Asp Phe His Ile Pro Glu
 1235 1240 1245
 Asn Leu Phe Leu Lys Ser Asp Gly Arg Val Lys Tyr Thr Leu Asn Lys
 1250 1255 1260
 Asn Ser Leu Lys Ile Glu Ile Pro Leu Pro Phe Gly Gly Lys Ser Ser
 1265 1270 1275 1280
 Arg Asp Leu Lys Met Leu Glu Thr Val Arg Thr Pro Ala Leu His Phe
 1285 1290 1295
 Lys Ser Val Gly Phe His Leu Pro Ser Arg Glu Phe Gln Val Pro Thr
 1300 1305 1310
 Phe Thr Ile Pro Lys Leu Tyr Gln Leu Gln Val Pro Leu Leu Gly Val
 1315 1320 1325
 Leu Asp Leu Ser Thr Asn Val Tyr Ser Asn Leu Tyr Asn Trp Ser Ala
 1330 1335 1340
 Ser Tyr Ser Gly Gly Asn Thr Ser Thr Asp His Phe Ser Leu Arg Ala
 1345 1350 1355 1360

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| | | |
|---|------|-----------|
| Arg Tyr His Met Lys Ala Asp Ser Val Val Asp Leu Leu Ser Tyr Asn | | |
| 1365 | 1370 | 1375 |
| Val Gln Gly Ser Gly Glu Thr Thr Tyr Asp His Lys Asn Thr Phe Thr | | |
| 1380 | 1385 | 1390 |
| Leu Ser Cys Asp Gly Ser Leu Arg His Lys Phe Leu Asp Ser Asn Ile | | |
| 1395 | 1400 | 1405 |
| Lys Phe Ser His Val Glu Lys Leu Gly Asn Asn Pro Val Ser Lys Gly | | |
| 1410 | 1415 | 1420 |
| Leu Leu Ile Phe Asp Ala Ser Ser Ser Trp Gly Pro Gln Met Ser Ala | | |
| 1425 | 1430 | 1435 1440 |
| Ser Val His Leu Asp Ser Lys Lys Lys Gln His Leu Phe Val Lys Glu | | |
| 1445 | 1450 | 1455 |
| Val Lys Ile Asp Gly Gln Phe Arg Val Ser Ser Phe Tyr Ala Lys Gly | | |
| 1460 | 1465 | 1470 |
| Thr Tyr Gly Leu Ser Cys Gln Arg Asp Pro Asn Thr Gly Arg Leu Asn | | |
| 1475 | 1480 | 1485 |
| Gly Glu Ser Asn Leu Arg Phe Asn Ser Ser Tyr Leu Gln Gly Thr Asn | | |
| 1490 | 1495 | 1500 |
| Gln Ile Thr Gly Arg Tyr Glu Asp Gly Thr Leu Ser Leu Thr Ser Thr | | |
| 1505 | 1510 | 1515 1520 |
| Ser Asp Leu Gln Ser Gly Ile Ile Lys Asn Thr Ala Ser Leu Lys Tyr | | |
| 1525 | 1530 | 1535 |
| Glu Asn Tyr Glu Leu Thr Leu Lys Ser Asp Thr Asn Gly Lys Tyr Lys | | |
| 1540 | 1545 | 1550 |
| Asn Phe Ala Thr Ser Asn Lys Met Asp Met Thr Phe Ser Lys Gln Asn | | |
| 1555 | 1560 | 1565 |
| Ala Leu Leu Arg Ser Glu Tyr Gln Ala Asp Tyr Glu Ser Leu Arg Phe | | |
| 1570 | 1575 | 1580 |
| Phe Ser Leu Leu Ser Gly Ser Leu Asn Ser His Gly Leu Glu Leu Asn | | |
| 1585 | 1590 | 1595 1600 |
| Ala Asp Ile Leu Gly Thr Asp Lys Ile Asn Ser Gly Ala His Lys Ala | | |
| 1605 | 1610 | 1615 |
| Thr Leu Arg Ile Gly Gln Asp Gly Ile Ser Thr Ser Ala Thr Thr Asn | | |
| 1620 | 1625 | 1630 |
| Leu Lys Cys Ser Leu Leu Val Leu Glu Asn Glu Leu Asn Ala Glu Leu | | |
| 1635 | 1640 | 1645 |

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|
| Gly | Leu | Ser | Gly | Ala | Ser | Met | Lys | Leu | Thr | Thr | Asn | Gly | Arg | Phe | Arg | 1650 | 1655 | 1660 | |
| Glu | His | Asn | Ala | Lys | Phe | Ser | Leu | Asp | Gly | Lys | Ala | Ala | Leu | Thr | Glu | 1665 | 1670 | 1675 | 1680 |
| Leu | Ser | Leu | Gly | Ser | Ala | Tyr | Gln | Ala | Met | Ile | Leu | Gly | Val | Asp | Ser | 1685 | 1690 | 1695 | |
| Lys | Asn | Ile | Phe | Asn | Phe | Lys | Val | Ser | Gln | Glu | Gly | Leu | Lys | Leu | Ser | 1700 | 1705 | 1710 | |
| Asn | Asp | Met | Met | Gly | Ser | Tyr | Ala | Glu | Met | Lys | Phe | Asp | His | Thr | Asn | 1715 | 1720 | 1725 | |
| Ser | Leu | Asn | Ile | Ala | Gly | Leu | Ser | Leu | Asp | Phe | Ser | Ser | Lys | Leu | Asp | 1730 | 1735 | 1740 | |
| Asn | Ile | Tyr | Ser | Ser | Asp | Lys | Phe | Tyr | Lys | Gln | Thr | Val | Asn | Leu | Gln | 1745 | 1750 | 1755 | 1760 |
| Leu | Gln | Pro | Tyr | Ser | Leu | Val | Thr | Thr | Leu | Asn | Ser | Asp | Leu | Lys | Tyr | 1765 | 1770 | 1775 | |
| Asn | Ala | Leu | Asp | Leu | Thr | Asn | Asn | Gly | Lys | Leu | Arg | Leu | Glu | Pro | Leu | 1780 | 1785 | 1790 | |
| Lys | Leu | His | Val | Ala | Gly | Asn | Leu | Lys | Gly | Ala | Tyr | Gln | Asn | Asn | Glu | 1795 | 1800 | 1805 | |
| Ile | Lys | His | Ile | Tyr | Ala | Ile | Ser | Ser | Ala | Ala | Leu | Ser | Ala | Ser | Tyr | 1810 | 1815 | 1820 | |
| Lys | Ala | Asp | Thr | Val | Ala | Lys | Val | Gln | Gly | Val | Glu | Phe | Ser | His | Arg | 1825 | 1830 | 1835 | 1840 |
| Leu | Asn | Thr | Asp | Ile | Ala | Gly | Leu | Ala | Ser | Ala | Ile | Asp | Met | Ser | Thr | 1845 | 1850 | 1855 | |
| Asn | Tyr | Asn | Ser | Asp | Ser | Leu | His | Phe | Ser | Asn | Val | Phe | Arg | Ser | Val | 1860 | 1865 | 1870 | |
| Met | Ala | Pro | Phe | Thr | Met | Thr | Ile | Asp | Ala | His | Thr | Asn | Gly | Asn | Gly | 1875 | 1880 | 1885 | |
| Lys | Leu | Ala | Leu | Trp | Gly | Glu | His | Thr | Gly | Gln | Leu | Tyr | Ser | Lys | Phe | 1890 | 1895 | 1900 | |
| Leu | Leu | Lys | Ala | Glu | Pro | Leu | Ala | Phe | Thr | Phe | Ser | His | Asp | Tyr | Lys | 1905 | 1910 | 1915 | 1920 |
| Gly | Ser | Thr | Ser | His | His | Leu | Val | Ser | Arg | Lys | Ser | Ile | Ser | Ala | Ala | 1925 | 1930 | 1935 | |

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Leu Glu His Lys Val Ser Ala Leu Leu Thr Pro Ala Glu Gln Thr Gly
 1940 1945 1950
 Thr Trp Lys Leu Lys Thr Gln Phe Asn Asn Asn Glu Tyr Ser Gln Asp
 1955 1960 1965
 Leu Asp Ala Tyr Asn Thr Lys Asp Lys Ile Gly Val Glu Leu Thr Gly
 1970 1975 1980
 Arg Thr Leu Ala Asp Leu Thr Leu Leu Asp Ser Pro Ile Lys Val Pro
 1985 1990 1995 2000
 Leu Leu Leu Ser Glu Pro Ile Asn Ile Ile Asp Ala Leu Glu Met Arg
 2005 2010 2015
 Asp Ala Val Glu Lys Pro Gln Glu Phe Thr Ile Val Ala Phe Val Lys
 2020 2025 2030
 Tyr Asp Lys Asn Gln Asp Val His Ser Ile Asn Leu Pro Phe Phe Glu
 2035 2040 2045
 Thr Leu Gln Glu Tyr Phe Glu Arg Asn Arg Gln Thr Ile Ile Val Val
 2050 2055 2060
 Val Glu Asn Val Gln Arg Asn Leu Lys His Ile Asn Ile Asp Gln Phe
 2065 2070 2075 2080
 Val Arg Lys Tyr Arg Ala Ala Leu Gly Lys Leu Pro Gln Gln Ala Asn
 2085 2090 2095
 Asp Tyr Leu Asn Ser Phe Asn Trp Glu Arg Gln Val Ser His Ala Lys
 2100 2105 2110
 Glu Lys Leu Thr Ala Leu Thr Lys Lys Tyr Arg Ile Thr Glu Asn Asp
 2115 2120 2125
 Ile Gln Ile Ala Leu Asp Asp Ala Lys Ile Asn Phe Asn Glu Lys Leu
 2130 2135 2140
 Ser Gln Leu Gln Thr Tyr Met Ile Gln Phe Asp Gln Tyr Ile Lys Asp
 2145 2150 2155 2160
 Ser Tyr Asp Leu His Asp Leu Lys Ile Ala Ile Ala Asn Ile Ile Asp
 2165 2170 2175
 Glu Ile Ile Glu Lys Leu Lys Ser Leu Asp Glu His Tyr His Ile Arg
 2180 2185 2190
 Val Asn Leu Val Lys Thr Ile His Asp Leu His Leu Phe Ile Glu Asn
 2195 2200 2205
 Ile Asp Phe Asn Lys Ser Gly Ser Ser Thr Ala Ser Trp Ile Gln Asn
 2210 2215 2220

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Val Asp Thr Lys Tyr Gln Ile Arg Ile Gln Ile Gln Glu Lys Leu Gln
 2225 2230 2235 2240
 Gln Leu Lys Arg His Ile Gln Asn Ile Asp Ile Gln His Leu Ala Gly
 2245 2250 2255
 Lys Leu Lys Gln His Ile Glu Ala Ile Asp Val Arg Val Leu Leu Asp
 2260 2265 2270
 Gln Leu Gly Thr Thr Ile Ser Phe Glu Arg Ile Asn Asp Val Leu Glu
 2275 2280 2285
 His Val Lys His Phe Val Ile Asn Leu Ile Gly Asp Phe Glu Val Ala
 2290 2295 2300
 Glu Lys Ile Asn Ala Phe Arg Ala Lys Val His Glu Leu Ile Glu Arg
 2305 2310 2315 2320
 Tyr Glu Val Asp Gln Gln Ile Gln Val Leu Met Asp Lys Leu Val Glu
 2325 2330 2335
 Leu Thr His Gln Tyr Lys Leu Lys Glu Thr Ile Gln Lys Leu Ser Asn
 2340 2345 2350
 Val Leu Gln Gln Val Lys Ile Lys Asp Tyr Phe Glu Lys Leu Val Gly
 2355 2360 2365
 Phe Ile Asp Asp Ala Val Lys Lys Leu Asn Glu Leu Ser Phe Lys Thr
 2370 2375 2380
 Phe Ile Glu Asp Val Asn Lys Phe Leu Asp Met Leu Ile Lys Lys Leu
 2385 2390 2395 2400
 Lys Ser Phe Asp Tyr His Gln Phe Val Asp Glu Thr Asn Asp Lys Ile
 2405 2410 2415
 Arg Glu Val Thr Gln Arg Leu Asn Gly Glu Ile Gln Ala Leu Glu Leu
 2420 2425 2430
 Pro Gln Lys Ala Glu Ala Leu Lys Leu Phe Leu Glu Glu Thr Lys Ala
 2435 2440 2445
 Thr Val Ala Val Tyr Leu Glu Ser Leu Gln Asp Thr Lys Ile Thr Leu
 2450 2455 2460
 Ile Ile Asn Trp Leu Gln Glu Ala Leu Ser Ser Ala Ser Leu Ala His
 2465 2470 2475 2480
 Met Lys Ala Lys Phe Arg Glu Thr Leu Glu Asp Thr Arg Asp Arg Met
 2485 2490 2495
 Tyr Asp Met Asp Ile Gln Gln Glu Leu Gln Arg Tyr Leu Ser Leu Val
 2500 2505 2510

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|
| Gly | Gln | Val | Tyr | Ser | Thr | Leu | Val | Thr | Tyr | Ile | Ser | Asp | Trp | Trp | Thr | 2515 | 2520 | 2525 | |
| Leu | Ala | Ala | Lys | Asn | Leu | Thr | Asp | Phe | Ala | Glu | Gln | Tyr | Ser | Ile | Gln | 2530 | 2535 | 2540 | |
| Asp | Trp | Ala | Lys | Arg | Met | Lys | Ala | Leu | Val | Glu | Gln | Gly | Phe | Thr | Val | 2545 | 2550 | 2555 | 2560 |
| Pro | Glu | Ile | Lys | Thr | Ile | Leu | Gly | Thr | Met | Pro | Ala | Phe | Glu | Val | Ser | 2565 | 2570 | 2575 | |
| Leu | Gln | Ala | Leu | Gln | Lys | Ala | Thr | Phe | Gln | Thr | Pro | Asp | Phe | Ile | Val | 2580 | 2585 | 2590 | |
| Pro | Leu | Thr | Asp | Leu | Arg | Ile | Pro | Ser | Val | Gln | Ile | Asn | Phe | Lys | Asp | 2595 | 2600 | 2605 | |
| Leu | Lys | Asn | Ile | Lys | Ile | Pro | Ser | Arg | Phe | Ser | Thr | Pro | Glu | Phe | Thr | 2610 | 2615 | 2620 | |
| Ile | Leu | Asn | Thr | Phe | His | Ile | Pro | Ser | Phe | Thr | Ile | Asp | Phe | Val | Glu | 2625 | 2630 | 2635 | 2640 |
| Met | Lys | Val | Lys | Ile | Ile | Arg | Thr | Ile | Asp | Gln | Met | Gln | Asn | Ser | Glu | 2645 | 2650 | 2655 | |
| Leu | Gln | Trp | Pro | Val | Pro | Asp | Ile | Tyr | Leu | Arg | Asp | Leu | Lys | Val | Glu | 2660 | 2665 | 2670 | |
| Asp | Ile | Pro | Leu | Ala | Arg | Ile | Thr | Leu | Pro | Asp | Phe | Arg | Leu | Pro | Glu | 2675 | 2680 | 2685 | |
| Ile | Ala | Ile | Pro | Glu | Phe | Ile | Ile | Pro | Thr | Leu | Asn | Leu | Asn | Asp | Phe | 2690 | 2695 | 2700 | |
| Gln | Val | Pro | Asp | Leu | His | Ile | Pro | Glu | Phe | Gln | Leu | Pro | His | Ile | Ser | 2705 | 2710 | 2715 | 2720 |
| His | Thr | Ile | Glu | Val | Pro | Thr | Phe | Gly | Lys | Leu | Tyr | Ser | Ile | Leu | Lys | 2725 | 2730 | 2735 | |
| Ile | Gln | Ser | Pro | Leu | Phe | Thr | Leu | Asp | Ala | Asn | Ala | Asp | Ile | Gly | Asn | 2740 | 2745 | 2750 | |
| Gly | Thr | Thr | Ser | Ala | Asn | Glu | Ala | Gly | Ile | Ala | Ala | Ser | Ile | Thr | Ala | 2755 | 2760 | 2765 | |
| Lys | Gly | Glu | Ser | Lys | Leu | Glu | Val | Leu | Asn | Phe | Asp | Phe | Gln | Ala | Asn | 2770 | 2775 | 2780 | |
| Ala | Gln | Leu | Ser | Asn | Pro | Lys | Ile | Asn | Pro | Leu | Ala | Leu | Lys | Glu | Ser | 2785 | 2790 | 2795 | 2800 |

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|
| Val | Lys | Phe | Ser | Ser | Lys | Tyr | Leu | Arg | Thr | Glu | His | Gly | Ser | Glu | Met | 2805 | 2810 | 2815 | |
| Leu | Phe | Phe | Gly | Asn | Ala | Ile | Glu | Gly | Lys | Ser | Asn | Thr | Val | Ala | Ser | 2820 | 2825 | 2830 | |
| Leu | His | Thr | Glu | Lys | Asn | Thr | Leu | Glu | Leu | Ser | Asn | Gly | Val | Ile | Val | 2835 | 2840 | 2845 | |
| Lys | Ile | Asn | Asn | Gln | Leu | Thr | Leu | Asp | Ser | Asn | Thr | Lys | Tyr | Phe | His | 2850 | 2855 | 2860 | |
| Lys | Leu | Asn | Ile | Pro | Lys | Leu | Asp | Phe | Ser | Ser | Gln | Ala | Asp | Leu | Arg | 2865 | 2870 | 2875 | 2880 |
| Asn | Glu | Ile | Lys | Thr | Leu | Leu | Lys | Ala | Gly | His | Ile | Ala | Trp | Thr | Ser | 2885 | 2890 | 2895 | |
| Ser | Gly | Lys | Gly | Ser | Trp | Lys | Trp | Ala | Cys | Pro | Arg | Phe | Ser | Asp | Glu | 2900 | 2905 | 2910 | |
| Gly | Thr | His | Glu | Ser | Gln | Ile | Ser | Phe | Thr | Ile | Glu | Gly | Pro | Leu | Thr | 2915 | 2920 | 2925 | |
| Ser | Phe | Gly | Leu | Ser | Asn | Lys | Ile | Asn | Ser | Lys | His | Leu | Arg | Val | Asn | 2930 | 2935 | 2940 | |
| Gln | Asn | Leu | Val | Tyr | Glu | Ser | Gly | Ser | Leu | Asn | Phe | Ser | Lys | Leu | Glu | 2945 | 2950 | 2955 | 2960 |
| Ile | Gln | Ser | Gln | Val | Asp | Ser | Gln | His | Val | Gly | His | Ser | Val | Leu | Thr | 2965 | 2970 | 2975 | |
| Ala | Lys | Gly | Met | Ala | Leu | Phe | Gly | Glu | Gly | Lys | Ala | Glu | Phe | Thr | Gly | 2980 | 2985 | 2990 | |
| Arg | His | Asp | Ala | His | Leu | Asn | Gly | Lys | Val | Ile | Gly | Thr | Leu | Lys | Asn | 2995 | 3000 | 3005 | |
| Ser | Leu | Phe | Phe | Ser | Ala | Gln | Pro | Phe | Glu | Ile | Thr | Ala | Ser | Thr | Asn | 3010 | 3015 | 3020 | |
| Asn | Glu | Gly | Asn | Leu | Lys | Val | Arg | Phe | Pro | Leu | Arg | Leu | Thr | Gly | Lys | 3025 | 3030 | 3035 | 3040 |
| Ile | Asp | Phe | Leu | Asn | Asn | Tyr | Ala | Leu | Phe | Leu | Ser | Pro | Ser | Ala | Gln | 3045 | 3050 | 3055 | |
| Gln | Ala | Ser | Trp | Gln | Val | Ser | Ala | Arg | Phe | Asn | Gln | Tyr | Lys | Tyr | Asn | 3060 | 3065 | 3070 | |
| Gln | Asn | Phe | Ser | Ala | Gly | Asn | Asn | Glu | Asn | Ile | Met | Glu | Ala | His | Val | 3075 | 3080 | 3085 | |

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Gly Ile Asn Gly Glu Ala Asn Leu Asp Phe Leu Asn Ile Pro Leu Thr
 3090 3095 3100
 Ile Pro Glu Met Arg Leu Pro Tyr Thr Ile Ile Thr Thr Pro Pro Leu
 3105 3110 3115 3120
 Lys Asp Phe Ser Leu Trp Glu Lys Thr Gly Leu Lys Glu Phe Leu Lys
 3125 3130 3135
 Thr Thr Lys Gln Ser Phe Asp Leu Ser Val Lys Ala Gln Tyr Lys Lys
 3140 3145 3150
 Asn Lys His Arg His Ser Ile Thr Asn Pro Leu Ala Val Leu Cys Glu
 3155 3160 3165
 Phe Ile Ser Gln Ser Ile Lys Ser Phe Asp Arg His Phe Glu Lys Asn
 3170 3175 3180
 Arg Asn Asn Ala Leu Asp Phe Val Thr Lys Ser Tyr Asn Glu Thr Lys
 3185 3190 3195 3200
 Ile Lys Phe Asp Lys Tyr Lys Ala Glu Lys Ser His Asp Glu Leu Pro
 3205 3210 3215
 Arg Thr Phe Gln Ile Pro Gly Tyr Thr Val Pro Val Val Asn Val Glu
 3220 3225 3230
 Val Ser Pro Phe Thr Ile Glu Met Ser Ala Phe Gly Tyr Val Phe Pro
 3235 3240 3245
 Lys Ala Val Ser Met Pro Ser Phe Ser Ile Leu Gly Ser Asp Val Arg
 3250 3255 3260
 Val Pro Ser Tyr Thr Leu Ile Leu Pro Ser Leu Glu Leu Pro Val Leu
 3265 3270 3275 3280
 His Val Pro Arg Asn Leu Lys Leu Ser Leu Pro His Phe Lys Glu Leu
 3285 3290 3295
 Cys Thr Ile Ser His Ile Phe Ile Pro Ala Met Gly Asn Ile Thr Tyr
 3300 3305 3310
 Asp Phe Ser Phe Lys Ser Ser Val Ile Thr Leu Asn Thr Asn Ala Glu
 3315 3320 3325
 Leu Phe Asn Gln Ser Asp Ile Val Ala His Leu Leu Ser Ser Ser Ser
 3330 3335 3340
 Ser Val Ile Asp Ala Leu Gln Tyr Lys Leu Glu Gly Thr Thr Arg Leu
 3345 3350 3355 3360
 Thr Arg Lys Arg Gly Leu Lys Leu Ala Thr Ala Leu Ser Leu Ser Asn
 3365 3370 3375

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Lys Phe Val Glu Gly Ser His Asn Ser Thr Val Ser Leu Thr Thr Lys
 3380 3385 3390
 Asn Met Glu Val Ser Val Ala Lys Thr Thr Lys Ala Glu Ile Pro Ile
 3395 3400 3405
 Leu Arg Met Asn Phe Lys Gln Glu Leu Asn Gly Asn Thr Lys Ser Lys
 3410 3415 3420
 Pro Thr Val Ser Ser Ser Met Glu Phe Lys Tyr Asp Phe Asn Ser Ser
 3425 3430 3435 3440
 Met Leu Tyr Ser Thr Ala Lys Gly Ala Val Asp His Lys Leu Ser Leu
 3445 3450 3455
 Glu Ser Leu Thr Ser Tyr Phe Ser Ile Glu Ser Ser Thr Lys Gly Asp
 3460 3465 3470
 Val Lys Gly Ser Val Leu Ser Arg Glu Tyr Ser Gly Thr Ile Ala Ser
 3475 3480 3485
 Glu Ala Asn Thr Tyr Leu Asn Ser Lys Ser Thr Arg Ser Ser Val Lys
 3490 3495 3500
 Leu Gln Gly Thr Ser Lys Ile Asp Asp Ile Trp Asn Leu Glu Val Lys
 3505 3510 3515 3520
 Glu Asn Phe Ala Gly Glu Ala Thr Leu Gln Arg Ile Tyr Ser Leu Trp
 3525 3530 3535
 Glu His Ser Thr Lys Asn His Leu Gln Leu Glu Gly Leu Phe Phe Thr
 3540 3545 3550
 Asn Gly Glu His Thr Ser Lys Ala Thr Leu Glu Leu Ser Pro Trp Gln
 3555 3560 3565
 Met Ser Ala Leu Val Gln Val His Ala Ser Gln Pro Ser Ser Phe His
 3570 3575 3580
 Asp Phe Pro Asp Leu Gly Gln Glu Val Ala Leu Asn Ala Asn Thr Lys
 3585 3590 3595 3600
 Asn Gln Lys Ile Arg Trp Lys Asn Glu Val Arg Ile His Ser Gly Ser
 3605 3610 3615
 Phe Gln Ser Gln Val Glu Leu Ser Asn Asp Gln Glu Lys Ala His Leu
 3620 3625 3630
 Asp Ile Ala Gly Ser Leu Glu Gly His Leu Arg Phe Leu Lys Asn Ile
 3635 3640 3645
 Ile Leu Pro Val Tyr Asp Lys Ser Leu Trp Asp Phe Leu Lys Leu Asp
 3650 3655 3660

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Val Thr Thr Ser Ile Gly Arg Arg Gln His Leu Arg Val Ser Thr Ala
 3665 3670 3675 3680

Phe Val Tyr Thr Lys Asn Pro Asn Gly Tyr Ser Phe Ser Ile Pro Val
 3685 3690 3695

Lys Val Leu Ala Asp Lys Phe Ile Thr Pro Gly Leu Lys Leu Asn Asp
 3700 3705 3710

Leu Asn Ser Val Leu Val Met Pro Thr Phe His Val Pro Phe Thr Asp
 3715 3720 3725

Leu Gln Val Pro Ser Cys Lys Leu Asp Phe Arg Glu Ile Gln Ile Tyr
 3730 3735 3740

Lys Lys Leu Arg Thr Ser Ser Phe Ala Leu Asn Leu Pro Thr Leu Pro
 3745 3750 3755 3760

Glu Val Lys Phe Pro Glu Val Asp Val Leu Thr Lys Tyr Ser Gln Pro
 3765 3770 3775

Glu Asp Ser Leu Ile Pro Phe Phe Glu Ile Thr Val Pro Glu Ser Gln
 3780 3785 3790

Leu Thr Val Ser Gln Phe Thr Leu Pro Lys Ser Val Ser Asp Gly Ile
 3795 3800 3805

Ala Ala Leu Asp Leu Asn Ala Val Ala Asn Lys Ile Ala Asp Phe Glu
 3810 3815 3820

Leu Pro Thr Ile Ile Val Pro Glu Gln Thr Ile Glu Ile Pro Ser Ile
 3825 3830 3835 3840

Lys Phe Ser Val Pro Ala Gly Ile Val Ile Pro Ser Phe Gln Ala Leu
 3845 3850 3855

Thr Ala Arg Phe Glu Val Asp Ser Pro Val Tyr Asn Ala Thr Trp Ser
 3860 3865 3870

Ala Ser Leu Lys Asn Lys Ala Asp Tyr Val Glu Thr Val Leu Asp Ser
 3875 3880 3885

Thr Cys Ser Ser Thr Val Gln Phe Leu Glu Tyr Glu Leu Asn Val Leu
 3890 3895 3900

Gly Thr His Lys Ile Glu Asp Gly Thr Leu Ala Ser Lys Thr Lys Gly
 3905 3910 3915 3920

Thr Leu Ala His Arg Asp Phe Ser Ala Glu Tyr Glu Glu Asp Gly Lys
 3925 3930 3935

Phe Glu Gly Leu Gln Glu Trp Glu Gly Lys Ala His Leu Asn Ile Lys
 3940 3945 3950

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Ser Pro Ala Phe Thr Asp Leu His Leu Arg Tyr Gln Lys Asp Lys Lys
 3955 3960 3965
 Gly Ile Ser Thr Ser Ala Ala Ser Pro Ala Val Gly Thr Val Gly Met
 3970 3975 3980
 Asp Met Asp Glu Asp Asp Asp Phe Ser Lys Trp Asn Phe Tyr Tyr Ser
 3985 3990 3995 4000
 Pro Gln Ser Ser Pro Asp Lys Lys Leu Thr Ile Phe Lys Thr Glu Leu
 4005 4010 4015
 Arg Val Arg Glu Ser Asp Glu Glu Thr Gln Ile Lys Val Asn Trp Glu
 4020 4025 4030
 Glu Glu Ala Ala Ser Gly Leu Leu Thr Ser Leu Lys Asp Asn Val Pro
 4035 4040 4045
 Lys Ala Thr Gly Val Leu Tyr Asp Tyr Val Asn Lys Tyr His Trp Glu
 4050 4055 4060
 His Thr Gly Leu Thr Leu Arg Glu Val Ser Ser Lys Leu Arg Arg Asn
 4065 4070 4075 4080
 Leu Gln Asn Asn Ala Glu Trp Val Tyr Gln Gly Ala Ile Arg Gln Ile
 4085 4090 4095
 Asp Asp Ile Asp Val Arg Phe Gln Lys Ala Ala Ser Gly Thr Thr Gly
 4100 4105 4110
 Thr Tyr Gln Glu Trp Lys Asp Lys Ala Gln Asn Leu Tyr Gln Glu Leu
 4115 4120 4125
 Leu Thr Gln Glu Gly Gln Ala Ser Phe Gln Gly Leu Lys Asp Asn Val
 4130 4135 4140
 Phe Asp Gly Leu Val Arg Val Thr Gln Lys Phe His Met Lys Val Lys
 4145 4150 4155 4160
 His Leu Ile Asp Ser Leu Ile Asp Phe Leu Asn Phe Pro Arg Phe Gln
 4165 4170 4175
 Phe Pro Gly Lys Pro Gly Ile Tyr Thr Arg Glu Glu Leu Cys Thr Met
 4180 4185 4190
 Phe Ile Arg Glu Val Gly Thr Val Leu Ser Gln Val Tyr Ser Lys Val
 4195 4200 4205
 His Asn Gly Ser Glu Ile Leu Phe Ser Tyr Phe Gln Asp Leu Val Ile
 4210 4215 4220
 Thr Leu Pro Phe Glu Leu Arg Lys His Lys Leu Ile Asp Val Ile Ser
 4225 4230 4235 4240

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| | | | |
|---|------|------|-----------|
| Met Tyr Arg Glu Leu Leu Lys Asp Leu Ser Lys Glu Ala Gln Glu Val | 4245 | 4250 | 4255 |
| Phe Lys Ala Ile Gln Ser Leu Lys Thr Thr Glu Val Leu Arg Asn Leu | 4260 | 4265 | 4270 |
| Gln Asp Leu Leu Gln Phe Ile Phe Gln Leu Ile Glu Asp Asn Ile Lys | 4275 | 4280 | 4285 |
| Gln Leu Lys Glu Met Lys Phe Thr Tyr Leu Ile Asn Tyr Ile Gln Asp | 4290 | 4295 | 4300 |
| Glu Ile Asn Thr Ile Phe Asn Asp Tyr Ile Pro Tyr Val Phe Lys Leu | 4305 | 4310 | 4315 4320 |
| Leu Lys Glu Asn Leu Cys Leu Asn Leu His Lys Phe Asn Glu Phe Ile | 4325 | 4330 | 4335 |
| Gln Asn Glu Leu Gln Glu Ala Ser Gln Glu Leu Gln Gln Ile His Gln | 4340 | 4345 | 4350 |
| Tyr Ile Met Ala Leu Arg Glu Glu Tyr Phe Asp Pro Ser Ile Val Gly | 4355 | 4360 | 4365 |
| Trp Thr Val Lys Tyr Tyr Glu Leu Glu Glu Lys Ile Val Ser Leu Ile | 4370 | 4375 | 4380 |
| Lys Asn Leu Leu Val Ala Leu Lys Asp Phe His Ser Glu Tyr Ile Val | 4385 | 4390 | 4395 4400 |
| Ser Ala Ser Asn Phe Thr Ser Gln Leu Ser Ser Gln Val Glu Gln Phe | 4405 | 4410 | 4415 |
| Leu His Arg Asn Ile Gln Glu Tyr Leu Ser Ile Leu Thr Asp Pro Asp | 4420 | 4425 | 4430 |
| Gly Lys Gly Lys Glu Lys Ile Ala Glu Leu Ser Ala Thr Ala Gln Glu | 4435 | 4440 | 4445 |
| Ile Ile Lys Ser Gln Ala Ile Ala Thr Lys Lys Ile Ile Ser Asp Tyr | 4450 | 4455 | 4460 |
| His Gln Gln Phe Arg Tyr Lys Leu Gln Asp Phe Ser Asp Gln Leu Ser | 4465 | 4470 | 4475 4480 |
| Asp Tyr Tyr Glu Lys Phe Ile Ala Glu Ser Lys Arg Leu Ile Asp Leu | 4485 | 4490 | 4495 |
| Ser Ile Gln Asn Tyr His Thr Phe Leu Ile Tyr Ile Thr Glu Leu Leu | 4500 | 4505 | 4510 |
| Lys Lys Leu Gln Ser Thr Thr Val Met Asn Pro Tyr Met Lys Leu Ala | 4515 | 4520 | 4525 |

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Pro Gly Glu Leu Thr Ile Ile Leu
4530 4535

(2) INFORMATION FOR SEQ ID NO: 2:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 3 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Pro Xaa Pro
1

(2) INFORMATION FOR SEQ ID NO: 3:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 46 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Lys Tyr Thr Tyr Asn Tyr Glu Ala Glu Ser Ser Ser Gly Val Pro Gly
1 5 10 15
 Thr Ala Asp Ser Arg Ser Ala Thr Arg Ile Asn Cys Lys Val Glu Leu
20 25 30
 Glu Val Pro Gln Leu Cys Ser Phe Ile Leu Lys Thr Ser Gln
35 40 45

(2) INFORMATION FOR SEQ ID NO: 4:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 45 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Ala Tyr Asp Phe Asn Tyr Pro Ile Lys Lys Asp Ser Ser Ser Gln Leu
1 5 10 15
 Leu Ser Val Gln Gln Gly Glu Thr Ile Tyr Ile Leu Asn Lys Asn Ser
20 25 30

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Ser Gly Trp Trp Asp Gly Leu Val Ile Asp Asp Ser Asn
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Val Tyr Gly Phe Asn Pro Glu Gly Lys Ala Leu Leu Lys Lys Thr Lys
 1 5 10 15

Asn Ser Glu Glu Phe Ala Ala Ala Met Ser Arg Tyr Glu Leu Lys Leu
 20 25 30

Ala Ile Pro Glu Gly Lys Gln Val Phe Leu Tyr Pro Glu
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 47 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn Thr Leu Ser Ile Thr Lys
 1 5 10 15

Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn His Tyr Asn Gly Glu Trp
 20 25 30

Cys Glu Ala Gln Thr Lys Asn Gly Gln Gly Trp Val Pro Ser Asn
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

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Phe Leu Pro Phe Ser Tyr Asn Asn Lys Tyr Gly Met Val Ala Gln Val
 1 5 10 15

Thr Gln Thr Leu Lys Leu Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe
 20 25 30

Phe Gly Glu Gly Thr Lys Lys Met Gly Leu Ala Phe
 35 40

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Leu Phe Asp Tyr Lys Ala Gln Arg Glu Asp Glu Leu Thr Phe Thr Lys
 1 5 10 15

Ser Ala Ile Ile Gln Asn Val Glu Lys Gln Glu Gly Gly Trp Trp Arg
 20 25 30

Gly Asp Tyr Gly Gly Lys Lys Gln Leu Trp Phe
 35 40

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Phe Leu Pro Phe Ser Tyr Asn Asn Lys Tyr Gly Met Val Ala Gln Val
 1 5 10 15

Thr Gln Thr Leu Lys Leu Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe
 20 25 30

Phe Gly Glu Gly Thr Lys Lys Met Gly Leu Ala Phe Glu
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 46 amino acids
- (B) TYPE: amino acid

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(C) STRANDEDNESS :

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Leu His Ser Tyr Glu Pro Ser His Asp Gly Asp Leu Gly Phe Glu Lys
1 5 10 15

Gly Glu Gln Leu Arg Ile Leu Glu Gln Ser Gly Glu Trp Trp Lys Ala
20 25 30

Gln Ser Leu Thr Thr Gly Gln Glu Gly Phe Ile Pro Phe Asn
35 40 45

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 62 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Tyr Thr Tyr Leu Ile Leu Arg Val Ile Gly Asn Met Gly Gln Thr Met
1 5 10 15

Glu Gln Leu Thr Pro Glu Leu Lys Ser Ser Ile Leu Lys Cys Val Gln
20 25 30

Ser Thr Lys Pro Ser Leu Met Ile Gln Lys Ala Ala Ile Gln Ala Leu
35 40 45

Arg Lys Met Glu Pro Lys Asp Lys Asp Gln Glu Val Leu Leu
50 55 60

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 53 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEO ID NO: 12:

Val Val Ala Leu Phe Asp Tyr Ala Ala Val Asn Asp Arg Asp Leu Gln
1 5 10 15

Val Leu Lys Gly Glu Lys Leu Gln Val Leu Arg Ser Thr Gly Asp Trp
20 25 30

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Trp Leu Ala Arg Ser Leu Val Thr Gly Arg Glu Gly Tyr Val Pro Ser
 35 40 45

Asn Phe Val Ala Pro
 50

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 50 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Ala Phe Gly Phe Ala Ser Ala Asp Leu Ile Glu Ile Gly Leu Glu Gly
 1 5 10 15

Lys Gly Phe Glu Pro Thr Leu Glu Ala Leu Phe Gly Lys Gln Gly Phe
 20 25 30

Phe Pro Asp Ser Val Asn Lys Ala Leu Tyr Trp Val Asn Gly Gln Val
 35 40 45

Pro Asp
 50

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Leu Tyr Asp Phe Ala Ala Glu Asn Pro Asp Glu Leu Thr Phe Asn Glu
 1 5 10 15

Gly Ala Val Val Thr Val Ile Asn Lys Ser Asn Pro Asp Trp Trp Glu
 20 25 30

Gly Glu Leu Asn Gly Gln Arg Gly Val Phe Pro Ala Ser Tyr Val Glu
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 46 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Gly | Tyr | Thr | Lys | Asp | Asp | Lys | His | Glu | Gln | Asp | Met | Val | Asn | Gly |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Ile | Met | Leu | Ser | Val | Glu | Lys | Leu | Ile | Lys | Asp | Leu | Lys | Ser | Lys | Glu |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Val | Pro | Glu | Ala | Arg | Ala | Tyr | Leu | Arg | Ile | Leu | Gly | Glu | Glu | | |
| | | 35 | | | | | 40 | | | | | 45 | | | |

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 49 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Asp | Tyr | Lys | Lys | Glu | Glu | Glu | Asp | Ile | Asp | Leu | His | Leu | Gly | Asp |
| 1 | | | 5 | | | | | | 10 | | | | | 15 | |
| Ile | Leu | Thr | Val | Asn | Lys | Gly | Ser | Leu | Val | Ala | Leu | Gly | Phe | Ser | Asp |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Gly | Gln | Glu | Ala | Lys | Pro | Glu | Glu | Ile | Gly | Trp | Leu | Asn | Gly | Tyr | Asn |
| | | 35 | | | | | 40 | | | | | 45 | | | |

Glu

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 52 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Asp | Tyr | His | Gln | Phe | Val | Asp | Glu | Thr | Asn | Asp | Lys | Ile | Arg | Glu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Val | Thr | Gln | Arg | Leu | Asn | Gly | Glu | Ile | Gln | Ala | Leu | Glu | Leu | Pro | Gln |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Lys | Ala | Glu | Ala | Leu | Lys | Leu | Phe | Leu | Glu | Glu | Thr | Lys | Ala | Thr | Val |
| | | 35 | | | | | 40 | | | | | 45 | | | |

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Ala Val Tyr Leu
50

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 46 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Asp | Tyr | Gln | Glu | Lys | Ser | Pro | Arg | Glu | Val | Thr | Met | Lys | Lys | Gly |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Asp | Ile | Leu | Thr | Leu | Leu | Asn | Ser | Thr | Asn | Lys | Asp | Trp | Trp | Lys | Val |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Glu | Val | Asn | Asp | Arg | Gln | Gly | Phe | Val | Pro | Ala | Ala | Tyr | Val | | |
| | | 35 | | | | 40 | | | | | | 45 | | | |

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Asp | Met | Asp | Ile | Gln | Gln | Glu | Leu | Gln | Arg | Tyr | Leu | Ser | Leu | Val |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Gly | Gln | Val | Tyr | Ser | Thr | Leu | Val | Thr | Tyr | Ile | Ser | Asp | Trp | Trp | Thr |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Leu | Ala | Ala | Lys | Asn | Leu | Thr | Asp | Phe | Ala | Glu | Gln | Tyr | Ser | Ile | Gln |
| | | 35 | | | | 40 | | | | | | 45 | | | |
| Asp | Trp | Ala | | | | | | | | | | | | | |
| | | 50 | | | | | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

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Phe Asp Tyr Lys Ala Gln Arg Glu Asp Glu Leu Thr Phe Thr Lys Ser
 1 5 10 15

Ala Ile Ile Gln Asn Val Glu Lys Gln Asp Gly Gly Trp Trp Arg Gly
 20 25 30

Asp Tyr Gly Gly Lys Lys Gln Leu Trp Phe Pro Ser Asn Tyr Val Glu
 35 40 45

Glu Met Ile
 50

(2) INFORMATION FOR SEQ ID NO: 21:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 55 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Tyr Asp Met Asp Ile Gln Gln Glu Leu Gln Arg Tyr Leu Ser Leu Val
 1 5 10 15

Gly Gln Val Tyr Ser Thr Leu Val Thr Tyr Ile Ser Asp Trp Trp Thr
 20 25 30

Leu Ala Ala Lys Asn Leu Thr Asp Phe Ala Glu Gln Tyr Ser Ile Gln
 35 40 45

Asp Trp Ala Lys Arg Met Lys
 50 55

(2) INFORMATION FOR SEQ ID NO: 22:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 53 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Ile Gln Asp Tyr Glu Pro Arg Leu Thr Asp Glu Ile Arg Ile Ser Leu
 1 5 10 15

Gly Glu Lys Val Lys Ile Leu Ala Thr His Thr Asp Gly Trp Cys Leu
 20 25 30

Val Glu Lys Cys Asn Thr Arg Lys Gly Thr Ile His Val Ser Val Asp
 35 40 45

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Asp Lys Arg Tyr Leu
50

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 49 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Tyr Asp Tyr Glu Ala Arg Thr Glu Asp Asp Leu Thr Phe Thr Lys Gly
1 5 10 15

Glu Lys Phe His Ile Leu Asn Asn Thr Glu Gly Asp Trp Trp Glu Ala
20 25 30

Arg Ser Leu Ser Ser Gly Lys Thr Gly Cys Ile Pro Ser Asn Tyr Val
35 40 45

Ala

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Thr Tyr Asp Phe Ser Phe Lys Ser Ser Val Ile Thr Leu Asn Thr Asn
1 5 10 15

Ala Glu Leu Phe Asn Gln Ser Asp Ile Val Ala His Leu Leu Ser Ser
20 25 30

Ser Ser Ser Val Ile Asp Ala Leu Gln Tyr Lys Leu Glu
35 40 45

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 47 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

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Asp Phe Asn Tyr Pro Ile Lys Lys Asp Ser Ser Ser Gln Leu Leu Ser
 1 5 10 15
 Val Gln Gln Gly Glu Thr Ile Tyr Ile Leu Asn Lys Asn Ser Ser Gly
 20 25 30
 Trp Trp Asp Gly Leu Val Ile Asp Asp Ser Asn Gly Lys Val Asn
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 49 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Lys Tyr Asp Phe Asn Ser Ser Met Leu Tyr Ser Thr Ala Lys Gly Ala
 1 5 10 15
 Val Asp His Lys Leu Ser Leu Glu Ser Leu Thr Ser Tyr Phe Ser Ile
 20 25 30
 Glu Ser Ser Thr Lys Gly Asp Val Lys Gly Ser Val Leu Ser Arg Glu
 35 40 45
 Tyr

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 52 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Glu Pro Tyr Val Ala Ile Lys Ala Tyr Thr Ala Val Glu Gly Asp Glu
 1 5 10 15
 Val Ser Leu Leu Glu Gly Glu Ala Val Glu Val Ile His Lys Leu Leu
 20 25 30
 Asp Gly Trp Trp Val Ile Arg Lys Asp Asp Val Thr Gly Tyr Phe Pro
 35 40 45
 Ser Met Tyr Leu
 50

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(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 54 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

```

Leu Trp Asp Phe Leu Lys Leu Asp Val Thr Thr Ser Ile Gly Arg Arg
1           5           10           15
Gln His Leu Arg Val Ser Thr Ala Phe Val Tyr Thr Lys Asn Pro Asn
          20           25           30
Gly Tyr Ser Phe Ser Ile Pro Val Lys Val Leu Ala Asp Lys Phe Ile
          35           40           45
Thr Pro Gly Leu Lys Leu
          50

```

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 55 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

```

Leu Tyr Asp Phe Lys Ala Glu Lys Ala Asp Glu Leu Thr Thr Tyr Val
1           5           10           15
Gly Glu Asn Leu Phe Ile Cys Ala His His Asn Cys Glu Trp Phe Ile
          20           25           30
Ala Lys Pro Ile Gly Arg Leu Gly Gly Pro Gly Leu Val Pro Val Gly
          35           40           45
Phe Val Ser Ile Ile Asp Ile
          50           55

```

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 47 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

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```

Val Leu Tyr Asp Tyr Val Asn Lys Tyr His Trp Glu His Thr Gly Leu
1              5              10              15

Thr Leu Arg Glu Val Ser Ser Lys Leu Arg Arg Asn Leu Gln Asn Asn
          20              25              30

Ala Glu Trp Val Tyr Gln Gly Ala Ile Arg Gln Ile Asp Asp Ile
      35              40              45

```

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

```

Val Leu Tyr Asp Phe Lys Ala Glu Lys Ala Asp Glu Leu Thr Thr Tyr
1              5              10              15

Val Gly Glu Asn Leu Phe Ile Cys Ala His His Asn Cys Glu Trp Phe
          20              25              30

Ile Ala Lys Pro Ile Gly Arg Leu
      35              40

```

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

```

Lys Pro Gly Ile Tyr Thr Arg Glu Glu Leu Cys Thr Met Phe Ile Arg
1              5              10              15

Glu Val Gly Thr Val Leu Ser Gln Val Tyr Ser Lys Val His Asn Gly
          20              25              30

Ser Glu Ile Leu Phe Ser Tyr Phe Gln Asp Leu
      35              40

```

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 52 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

```

Leu Phe Gly Phe Val Pro Glu Thr Lys Glu Glu Leu Gln Val Met Pro
1           5           10           15

Gly Asn Ile Val Phe Val Leu Lys Lys Gly Asn Asp Asn Trp Ala Thr
          20           25           30

Val Met Phe Asn Gly Gln Lys Gly Leu Val Pro Cys Asn Tyr Leu Glu
          35           40           45

Pro Val Glu Leu
          50

```

(2) INFORMATION FOR SEQ ID NO: 34:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 43 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

```

Gly Lys Pro Gly Ile Tyr Thr Arg Glu Glu Leu Cys Thr Met Phe Ile
1           5           10           15

Arg Glu Val Gly Thr Val Leu Ser Gln Val Tyr Ser Lys Val His Asn
          20           25           30

Gly Ser Glu Ile Leu Phe Ser Tyr Phe Gln Asp
          35           40

```

(2) INFORMATION FOR SEQ ID NO: 35:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 52 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

```

Ala Lys Phe Asp Tyr Val Ala Gln Gln Glu Gln Glu Leu Asp Ile Lys
1           5           10           15

Lys Asn Glu Arg Leu Trp Leu Leu Asp Asp Ser Lys Ser Trp Trp Arg
          20           25           30

Val Arg Asn Ser Met Asn Lys Thr Gly Phe Val Pro Ser Asn Tyr Val
          35           40           45

```

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Glu Arg Lys Asn
50

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 85 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|
| Trp | Tyr | His | Ala | Ser | Leu | Thr | Arg | Ala | Gln | Ala | Glu | His | Met | Leu | Met | 1 | 5 | 10 | 15 |
| Arg | Val | Pro | Arg | Asp | Gly | Ala | Phe | Leu | Val | Arg | Lys | Arg | Asn | Glu | Pro | 20 | 25 | 30 | |
| Asn | Ser | Tyr | Ala | Ile | Ser | Phe | Arg | Ala | Glu | Gly | Lys | Ile | Lys | His | Cys | 35 | 40 | 45 | |
| Arg | Val | Gln | Gln | Glu | Gly | Thr | Val | Met | Leu | Gly | Asn | Ser | Glu | Phe | Asp | 50 | 55 | 60 | |
| Ser | Leu | Val | Asp | Leu | Ile | Ser | Tyr | Tyr | Glu | Lys | His | Pro | Leu | Tyr | Arg | 65 | 70 | 75 | 80 |
| Lys | Met | Lys | Leu | Lys | | | | | | | | | | | | 85 | | | |

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 106 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|
| Phe | Phe | Gly | Glu | Gly | Thr | Lys | Lys | Met | Gly | Leu | Ala | Phe | Glu | Ser | Thr | 1 | 5 | 10 | 15 |
| Lys | Ser | Thr | Ser | Pro | Pro | Lys | Gln | Ala | Glu | Ala | Val | Leu | Lys | Thr | Leu | 20 | 25 | 30 | |
| Gln | Glu | Leu | Lys | Lys | Leu | Thr | Ile | Ser | Glu | Gln | Asn | Ile | Gln | Arg | Ala | 35 | 40 | 45 | |
| Asn | Leu | Phe | Asn | Lys | Leu | Val | Thr | Glu | Leu | Arg | Gly | Leu | Ser | Asp | Glu | 50 | 55 | 60 | |

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Ala Val Thr Ser Leu Leu Pro Gln Leu Ile Glu Val Ser Ser Pro Ile
65 70 75 80

Thr Leu Gln Ala Leu Val Gln Cys Gly Gln Pro Cys Ser Thr His Ile
85 90 95

Leu Gln Trp Leu Lys Arg Val His Ala Asn
100 105

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 91 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Trp Phe His Gly Lys Ile Ser Lys Gln Glu Ala Tyr Asn Leu Leu Met
1 5 10 15

Thr Val Gly Gln Ala Cys Ser Phe Leu Val Arg Pro Ser Asp Asn Thr
20 25 30

Pro Gly Asp Tyr Ser Leu Tyr Phe Arg Thr Ser Glu Asn Ile Gln Arg
35 40 45

Phe Lys Ile Cys Pro Thr Pro Asn Asn Gln Phe Met Met Gly Gly Arg
50 55 60

Tyr Tyr Asn Ser Ser Ile Gly Asp Ile Ile Asp His Tyr Arg Lys Glu
65 70 75 80

Gln Ile Val Glu Gly Tyr Tyr Leu Lys Glu Pro
85 90

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 93 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

Ile Met Leu Ser Val Glu Lys Leu Ile Lys Asp Leu Lys Ser Lys Glu
1 5 10 15

Val Pro Glu Ala Arg Ala Tyr Leu Arg Ile Leu Gly Glu Glu Leu Gly
20 25 30

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Ala | Ser | Leu | His | Asp | Leu | Gln | Leu | Leu | Gly | Lys | Leu | Leu | Leu | Met |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Gly | Ala | Arg | Thr | Leu | Gln | Gly | Ile | Pro | Gln | Met | Ile | Gly | Glu | Val | Ile |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Arg | Lys | Gly | Ser | Lys | Asn | Asp | Phe | Phe | Leu | His | Tyr | Ile | Phe | Met | Glu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Asn | Ala | Phe | Glu | Leu | Pro | Thr | Gly | Ala | Gly | Leu | Gln | Leu | | | |
| | | | 85 | | | | | 90 | | | | | | | |

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 89 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

[illegible]

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 77 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

Tyr Phe His Lys Leu Asn Ile Pro Lys Leu Asp Phe Ser Ser Gln Ala
1 5 10 15

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Asp Leu Arg Asn Glu Ile Lys Thr Leu Leu Lys Ala Gly His Ile Ala
 20 25 30

Trp Thr Ser Ser Gly Lys Gly Ser Trp Lys Trp Ala Cys Pro Arg Phe
 35 40 45

Ser Asp Glu Gly Thr His Glu Ser Gln Ile Ser Phe Thr Ile Glu Gly
 50 55 60

Pro Leu Thr Ser Phe Gly Leu Ser Asn Lys Ile Asn Ser
 65 70 75

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 99 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Trp Tyr Trp Gly Asp Ile Ser Arg Glu Glu Val Asn Glu Lys Leu Arg
 1 5 10 15

Asp Thr Pro Asp Gly Thr Phe Leu Val Arg Asp Ala Ser Ser Lys Ile
 20 25 30

Gln Gly Asp Tyr Thr Leu Thr Leu Arg Lys Gly Gly Asn Asn Lys Leu
 35 40 45

Ile Lys Val Phe His Arg Asp Gly Lys Tyr Gly Phe Ser Glu Pro Leu
 50 55 60

Thr Phe Cys Ser Val Val Asp Leu Ile Thr His Tyr Arg His Glu Ser
 65 70 75 80

Leu Ala Gln Tyr Asn Ala Lys Leu Asp Thr Arg Leu Leu Tyr Pro Val
 85 90 95

Ser Lys Tyr

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

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```

Phe Phe Ser Ala Gln Pro Phe Glu Ile Thr Ala Ser Thr Asn Asn Glu
1           5           10           15
Gly Asn Leu Lys Val Arg Phe Pro Leu Arg Leu Thr Gly Lys Ile Asp
          20           25           30
Phe Leu Asn Asn Tyr Ala Leu Phe Leu Ser Pro Ser Ala Gln Gln Ala
          35           40           45
Ser Trp Gln Val Ser Ala Arg Phe Asn Gln Tyr Lys Tyr Asn Gln Asn
          50           55           60
Phe Ser Ala Gly Asn Asn Glu Asn Ile Met Glu Ala His Val Gly Ile
65           70           75           80
Asn Gly Glu Ala Asn Leu Asp Phe Leu Asn Ile Pro Leu Thr Ile Pro
          85           90           95
Glu Met Arg Leu
          100

```

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 106 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

```

Trp Phe His Gly Lys Leu Gly Ala Gly Arg Asp Gly Arg His Ile Ala
1           5           10           15
Glu Arg Leu Leu Thr Glu Tyr Cys Ile Glu Thr Gly Ala Pro Asp Gly
          20           25           30
Ser Phe Leu Val Arg Glu Ser Glu Thr Phe Val Gly Asp Tyr Thr Leu
          35           40           45
Ser Phe Trp Arg Asn Gly Lys Val Gln His Cys Arg Ile His Ser Arg
          50           55           60
Gln Asp Ala Gly Thr Pro Lys Phe Phe Leu Thr Asp Asn Leu Val Phe
65           70           75           80
Asp Ser Leu Tyr Asp Leu Ile Thr His Tyr Gln Gln Val Pro Leu Arg
          85           90           95
Cys Asn Glu Phe Glu Met Arg Leu Ser Glu
          100           105

```

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(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 91 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

```

Phe Pro Gly Lys Pro Gly Ile Tyr Thr Arg Glu Glu Leu Cys Thr Met
1           5           10           15
Phe Ile Arg Glu Val Gly Thr Val Leu Ser Gln Val Tyr Ser Lys Val
          20           25           30
His Asn Gly Ser Glu Ile Leu Phe Ser Tyr Phe Gln Asp Leu Val Ile
          35           40           45
Thr Leu Pro Phe Glu Leu Arg Lys His Lys Leu Ile Asp Val Ile Ser
50           55           60
Met Tyr Arg Glu Leu Leu Lys Asp Leu Ser Lys Glu Ala Gln Glu Val
65           70           75           80
Phe Lys Ala Ile Gln Ser Leu Lys Thr Thr Glu
          85           90

```

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 203 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

```

Val Ser Asp Gly Ile Ala Ala Leu Asp Leu Asn Ala Val Ala Asn Lys
1           5           10           15
Ile Ala Asp Phe Glu Leu Pro Thr Ile Ile Val Pro Glu Gln Thr Ile
          20           25           30
Glu Ile Pro Ser Ile Lys Phe Ser Val Pro Ala Gly Ile Val Ile Pro
          35           40           45
Ser Phe Gln Ala Leu Thr Ala Arg Phe Glu Val Asp Ser Pro Val Tyr
50           55           60
Asn Ala Thr Trp Ser Ala Ser Leu Lys Asn Lys Ala Asp Tyr Val Glu
65           70           75           80
Thr Val Leu Asp Ser Thr Cys Ser Ser Thr Val Gln Phe Leu Glu Tyr
          85           90           95

```

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| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Glu | Leu | Asn | Val | Leu | Gly | Thr | His | Lys | Ile | Glu | Asp | Gly | Thr | Leu | Ala | |
| | | | 100 | | | | | | 105 | | | | 110 | | | |
| Ser | Lys | Thr | Lys | Gly | Thr | Leu | Ala | His | Arg | Asp | Phe | Ser | Ala | Glu | Tyr | |
| | | 115 | | | | | 120 | | | | | 125 | | | | |
| Glu | Glu | Asp | Gly | Lys | Phe | Glu | Gly | Leu | Gln | Glu | Trp | Glu | Gly | Lys | Ala | |
| | 130 | | | | | | 135 | | | | 140 | | | | | |
| His | Leu | Asn | Ile | Lys | Ser | Pro | Ala | Phe | Thr | Asp | Leu | His | Leu | Arg | Tyr | |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| Gln | Lys | Asp | Lys | Lys | Gly | Ile | Ser | Thr | Ser | Ala | Ala | Ser | Pro | Ala | Val | |
| | | | | 165 | | | | | 170 | | | | | | 175 | |
| Gly | Thr | Val | Gly | Met | Asp | Met | Asp | Glu | Asp | Asp | Asp | Phe | Ser | Lys | Trp | |
| | | | 180 | | | | | 185 | | | | | 190 | | | |
| Asn | Phe | Tyr | Tyr | Ser | Pro | Gln | Ser | Ser | Pro | Asp | | | | | | |
| | | 195 | | | | | 200 | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 214 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Leu | Gly | Gln | Gly | Cys | Phe | Gly | Glu | Val | Trp | Met | Gly | Thr | Trp | Asn | Gly | |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | | |
| Thr | Thr | Arg | Val | Ala | Ile | Lys | Thr | Leu | Lys | Pro | Gly | Thr | Met | Ser | Pro | |
| | | | 20 | | | | | 25 | | | | | 30 | | | |
| Glu | Ala | Phe | Leu | Gln | Glu | Ala | Gln | Val | Met | Lys | Lys | Leu | Arg | His | Glu | |
| | 35 | | | | | | 40 | | | | | 45 | | | | |
| Lys | Leu | Val | Gln | Leu | Tyr | Ala | Val | Val | Ser | Glu | Glu | Pro | Ile | Tyr | Ile | |
| | 50 | | | | | 55 | | | | | 60 | | | | | |
| Val | Thr | Glu | Tyr | Met | Ser | Lys | Gly | Ser | Leu | Leu | Asp | Phe | Leu | Lys | Gly | |
| 65 | | | | 70 | | | | | 75 | | | | | 80 | | |
| Glu | Thr | Gly | Lys | Tyr | Leu | Arg | Leu | Pro | Gln | Leu | Val | Asp | Met | Ala | Ala | |
| | | | 85 | | | | | 90 | | | | | 95 | | | |
| Gln | Ile | Ala | Ser | Gly | Met | Ala | Tyr | Val | Glu | Arg | Met | Asn | Tyr | Val | His | |
| | | 100 | | | | | | 105 | | | | | 110 | | | |
| Arg | Asp | Leu | Arg | Ala | Ala | Asn | Ile | Leu | Val | Gly | Glu | Asn | Leu | Val | Cys | |
| | | 115 | | | | | 120 | | | | | 125 | | | | |

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Lys Val Ala Asp Phe Gly Leu Ala Arg Leu Ile Glu Asp Asn Glu Tyr
 130 135 140
 Thr Ala Arg Gln Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu
 145 150 155 160
 Ala Ala Leu Tyr Gly Arg Phe Thr Ile Lys Ser Asp Val Trp Ser Phe
 165 170 175
 Gly Ile Leu Leu Thr Glu Leu Thr Thr Lys Gly Arg Val Pro Tyr Pro
 180 185 190
 Gly Met Val Asn Arg Glu Val Leu Asp Gln Val Glu Arg Gly Tyr Arg
 195 200 205
 Met Pro Cys Pro Pro Glu
 210

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 213 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Leu Gly Asn Gly Gln Phe Gly Glu Val Trp Met Gly Thr Trp Asn Gly
 1 5 10 15
 Asn Thr Lys Val Ala Ile Lys Thr Leu Lys Pro Gly Thr Met Ser Pro
 20 25 30
 Glu Ser Phe Leu Glu Glu Ala Gln Ile Met Lys Lys Leu Lys His Asp
 35 40 45
 Lys Leu Val Gln Leu Tyr Ala Val Val Ser Glu Glu Pro Ile Tyr Ile
 50 55 60
 Val Thr Glu Tyr Met Asn Lys Gly Ser Leu Leu Asp Phe Leu Lys Asp
 65 70 75 80
 Gly Glu Gly Arg Ala Leu Lys Leu Pro Asn Leu Val Asp Met Ala Ala
 85 90 95
 Gln Val Ala Ala Gly Met Ala Tyr Ile Glu Arg Met Asn Tyr Ile His
 100 105 110
 Arg Asp Leu Arg Ser Ala Asn Ile Leu Val Gly Asn Gly Leu Ile Cys
 115 120 125
 Lys Ile Ala Asp Phe Gly Leu Ala Arg Leu Ile Glu Asp Asn Glu Tyr
 130 135 140

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Thr Ala Arg Gln Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu
 145 150 155 160

Ala Ala Leu Tyr Gly Arg Phe Thr Ile Lys Ser Asp Val Trp Ser Phe
 165 170 175

Gly Ile Leu Leu Thr Glu Leu Val Thr Lys Gly Arg Val Pro Tyr Pro
 180 185 190

Gly Met Asn Asn Arg Glu Val Leu Glu Gln Val Glu Arg Gly Tyr Arg
 195 200 205

Met Pro Cys Pro Gln
 210

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 213 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Leu Gly Ala Gly Gln Phe Gly Glu Val Trp Met Ala Thr Tyr Asn Lys
 1 5 10 15

His Thr Lys Val Ala Val Lys Thr Met Lys Pro Gly Ser Met Ser Val
 20 25 30

Glu Ala Phe Leu Ala Glu Ala Asn Val Met Lys Thr Leu Gln His Asp
 35 40 45

Lys Leu Val Lys Leu His Ala Val Val Thr Lys Glu Pro Ile Tyr Ile
 50 55 60

Ile Thr Glu Phe Met Ala Lys Gly Ser Leu Leu Asp Phe Leu Lys Ser
 65 70 75 80

Asp Glu Gly Ser Lys Gln Pro Leu Pro Lys Leu Ile Asp Phe Ser Ala
 85 90 95

Gln Ile Ala Glu Gly Met Ala Phe Ile Glu Gln Arg Asn Tyr Ile His
 100 105 110

Arg Asp Leu Arg Ala Ala Asn Ile Leu Val Ser Ala Ser Leu Val Cys
 115 120 125

Lys Ile Ala Asp Phe Gly Leu Ala Arg Val Ile Glu Asp Asn Glu Tyr
 130 135 140

Thr Ala Arg Glu Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu
 145 150 155 160

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Ala Ile Asn Phe Gly Ser Phe Thr Ile Lys Ser Asp Val Trp Ser Phe
 165 170 175

Gly Ile Leu Leu Met Glu Ile Val Thr Tyr Gly Arg Ile Pro Tyr Pro
 180 185 190

Gly Met Ser Asn Pro Glu Val Ile Arg Ala Leu Glu Arg Gly Tyr Arg
 195 200 205

Met Pro Arg Pro Glu
 210

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 218 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Leu Gly Ala Gly Gln Phe Gly Glu Val Trp Met Gly Tyr Tyr Asn Asn
 1 5 10 15

Ser Thr Lys Val Ala Val Lys Thr Leu Lys Pro Gly Thr Met Ser Val
 20 25 30

Gln Ala Phe Leu Glu Glu Ala Asn Leu Met Lys Thr Leu Gln His Asp
 35 40 45

Lys Leu Val Arg Leu Tyr Ala Val Val Thr Arg Glu Glu Pro Ile Tyr
 50 55 60

Ile Ile Thr Glu Tyr Met Ala Lys Gly Ser Leu Leu Asp Phe Leu Lys
 65 70 75 80

Ser Asp Glu Gly Gly Lys Val Leu Leu Pro Lys Leu Ile Asp Phe Ser
 85 90 95

Ala Gln Ile Ala Glu Gly Met Ala Tyr Ile Glu Arg Lys Asn Tyr Ile
 100 105 110

His Arg Asp Leu Arg Ala Ala Asn Val Leu Val Ser Glu Ser Leu Met
 115 120 125

Cys Lys Ile Ala Asp Phe Gly Leu Ala Arg Val Ile Glu Asp Asn Glu
 130 135 140

Tyr Thr Ala Arg Glu Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro
 145 150 155 160

Glu Ala Ile Asn Phe Gly Cys Phe Thr Ile Lys Ser Asp Val Trp Ser
 165 170 175

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Phe Gly Ile Leu Leu Tyr Glu Ile Val Thr Tyr Gly Lys Ile Pro Tyr
 180 185 190

Pro Gly Arg Thr Asn Ala Asp Val Met Thr Ala Leu Ser Gln Gly Tyr
 195 200 205

Arg Met Pro Arg Val Glu Asn Cys Pro Asp
 210 215

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 213 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Leu Gly Ala Gly Gln Phe Gly Glu Val Trp Met Gly Tyr Tyr Asn Gly
 1 5 10 15

His Thr Lys Val Ala Val Lys Ser Leu Lys Gln Gly Ser Met Ser Pro
 20 25 30

Asp Ala Phe Leu Ala Glu Ala Asn Leu Met Lys Gln Leu Gln His Gln
 35 40 45

Arg Leu Val Arg Leu Tyr Ala Val Val Thr Gln Glu Pro Ile Tyr Ile
 50 55 60

Ile Thr Glu Tyr Met Glu Asn Gly Ser Leu Val Asp Phe Leu Lys Thr
 65 70 75 80

Pro Ser Gly Ile Lys Leu Thr Ile Asn Lys Leu Leu Asp Met Ala Ala
 85 90 95

Gln Ile Ala Glu Gly Met Ala Phe Ile Glu Glu Arg Asn Tyr Ile His
 100 105 110

Arg Asp Leu Arg Ala Ala Asn Ile Leu Val Ser Asp Thr Leu Ser Cys
 115 120 125

Lys Ile Ala Asp Phe Gly Leu Ala Arg Leu Ile Glu Asp Asn Glu Tyr
 130 135 140

Thr Ala Arg Glu Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu
 145 150 155 160

Ala Ile Asn Tyr Gly Thr Phe Thr Ile Lys Ser Asp Val Trp Ser Phe
 165 170 175

Gly Ile Leu Leu Thr Glu Ile Val Thr His Gly Arg Ile Pro Tyr Pro
 180 185 190

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Gly Met Thr Asn Pro Glu Val Ile Gln Asn Leu Glu Arg Gly Tyr Arg
195 200 205

Met Val Arg Pro Asp
210

(2) INFORMATION FOR SEQ ID NO: 52:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

Arg Lys Asn Tyr Ile His Arg Asp Leu Arg Ala Ala Asn
1 5 10

(2) INFORMATION FOR SEQ ID NO: 53:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

Lys Gly Thr Leu Ala His Arg Asp Phe Ser Ala Glu
1 5 10

(2) INFORMATION FOR SEQ ID NO: 54:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

Thr Lys Val Ala Val Lys Thr Leu Lys Pro Gly
1 5 10

(2) INFORMATION FOR SEQ ID NO: 55:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

| | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Lys | Val | Ala | Ile | Lys | Thr | Ile | Arg | Glu | Gly |
| 1 | | | | 5 | | | | | 10 | |

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 11 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

| | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Leu | Asn | Ala | Val | Ala | Asn | Lys | Ile | Ala | Asp |
| 1 | | | | 5 | | | | | 10 | |

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Ser | Leu | Arg | Ala | Pro | Thr | Met | Pro | Pro | Pro | Leu | Pro | Pro | Val | Pro |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Pro | Gln | Pro | Ala | Arg | Arg | Gln | Ser | Arg | Arg | Leu | Pro | Ala | Ser | Pro | Val |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Ile | Ser | | | | | | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Asp | Ala | Glu | Gly | Thr | Ala | Val | Ala | Pro | Pro | Thr | Val | Thr | Pro | Val |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

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Pro Ser Leu Glu Ala Pro Ser Glu Gln Ala Pro Thr Glu Gln Arg Pro
 20 25 30

Gly Val Gln Glu
 35

(2) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

Ser Asp Ala Glu Gly Thr Ala Val Ala Pro Pro Thr Ile Thr Pro Ile
 1 5 10 15

Pro Ser Leu Glu Ala Pro Ser Glu Gln Ala Pro Thr Glu Gln Arg Pro
 20 25 30

Gly Val Gln Glu
 35

(2) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

Ser Asp Ala Glu Trp Thr Ala Phe Val Pro Pro Asn Val Ile Leu Ala
 1 5 10 15

Pro Ser Leu Glu Ala Phe Phe Glu Gln Ala Leu Thr Glu Glu Thr Pro
 20 25 30

Gly Val Gln Asp
 35

(2) INFORMATION FOR SEQ ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

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Leu Val Thr Glu Ser Ser Val Leu Ala Thr Leu Thr Val Val Pro Asp
 1 5 10 15
 Pro Ser Thr Glu Ala Ser Ser Glu Glu Ala Pro Thr Glu Gln Ser Pro
 20 25 30
 Gly Val Gln Asp
 35

(2) INFORMATION FOR SEQ ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

Pro Val Met Glu Ser Thr Leu Leu Thr Thr Pro Thr Val Val Pro Val
 1 5 10 15
 Pro Ser Thr Glu Leu Pro Ser Glu Glu Ala Pro Thr Glu Asn Ser Thr
 20 25 30
 Gly Val Gln Asp
 35

(2) INFORMATION FOR SEQ ID NO: 63:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 63:

Pro Val Thr Glu Ser Ser Val Leu Thr Thr Pro Thr Val Ala Pro Val
 1 5 10 15
 Pro Ser Thr Glu Ala Pro Ser Glu Gln Ala Pro Pro Glu Lys Ser Pro
 20 25 30
 Val Val Gln Asp
 35

(2) INFORMATION FOR SEQ ID NO: 64:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid

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(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Glu | Thr | Glu | Ser | Gly | Val | Leu | Glu | Thr | Pro | Thr | Val | Val | Pro | Glu |
| 1 | | | | 5 | | | | 10 | | | | | 15 | | |
| Pro | Ser | Met | Glu | Ala | His | Ser | Glu | Ala | Ala | Pro | Thr | Glu | Gln | Thr | Pro |
| | | | 20 | | | | 25 | | | | | 30 | | | |
| Val | Val | Arg | Gln | | | | | | | | | | | | |
| | | | 35 | | | | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 65:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Asp | Thr | Glu | Ser | Gly | Thr | Val | Val | Ala | Pro | Pro | Thr | Val | Ile | Gln |
| 1 | | | | 5 | | | | 10 | | | | | 15 | | |
| Val | Pro | Ser | Leu | Gly | Pro | Pro | Ser | Glu | Gln | Asp | | | | | |
| | | | 20 | | | | 25 | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 66:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 37 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Lys | Asp | Ala | Thr | Arg | Phe | Lys | His | Leu | Arg | Lys | Tyr | Thr | Tyr | Asn |
| 1 | | | | 5 | | | | 10 | | | | | 15 | | |
| Tyr | Glu | Ala | Glu | Ser | Ser | Ser | Gly | Val | Pro | Gly | Thr | Ala | Asp | Ser | Arg |
| | | | 20 | | | | 25 | | | | | 30 | | | |
| Ser | Ala | Thr | Arg | Ile | | | | | | | | | | | |
| | | | 35 | | | | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 34 amino acids

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- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

Pro Lys Asp Ala Ser Gln Arg Arg Arg Ser Leu Glu Pro Ala Glu Asn
 1 5 10 15

Val His Gly Ala Gly Gly Gly Ala Phe Pro Ala Ser Gln Thr Pro Ser
 20 25 30

Lys Pro

(2) INFORMATION FOR SEQ ID NO: 68:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 32 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

Asp Lys Glu Ala Thr Lys Leu Thr Glu Glu Arg Asp Gly Ser Leu Asn
 1 5 10 15

Gln Ser Ser Gly Tyr Arg Tyr Gly Thr Asp Pro Thr Pro Gln His Tyr
 20 25 30

(2) INFORMATION FOR SEQ ID NO: 69:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 39 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

Ile Gln Asn Tyr His Thr Phe Leu Ile Tyr Ile Thr Glu Leu Leu Lys
 1 5 10 15

Lys Leu Gln Ser Thr Thr Val Met Asn Pro Tyr Met Lys Leu Ala Pro
 20 25 30

Gly Glu Leu Thr Ile Ile Leu
 35

(2) INFORMATION FOR SEQ ID NO: 70:

- (i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Glu | Glu | Arg | Pro | Thr | Phe | Glu | Tyr | Leu | Gln | Ala | Phe | Leu | Glu | Asp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Tyr | Phe | Thr | Ser | Thr | Glu | Pro | Gln | Tyr | Gln | Pro | Gly | Glu | Asn | Leu | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 71:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 31 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Glu | Glu | Arg | Pro | Thr | Phe | Glu | Tyr | Leu | Gln | Ser | Phe | Leu | Glu | Asp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Tyr | Phe | Thr | Ala | Thr | Glu | Pro | Gln | Tyr | Gln | Pro | Gly | Glu | Asn | Leu | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 72:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Glu | Glu | Arg | Pro | Thr | Phe | Glu | Tyr | Ile | Gln | Ser | Val | Leu | Asp | Asp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Phe | Tyr | Thr | Ala | Thr | Glu | Ser | Gln | Tyr | Gln | Gln | Gln | Pro | | | |
| | | | 20 | | | | | 25 | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 73:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 29 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Glu | Glu | Arg | Pro | Thr | Phe | Asp | Tyr | Leu | Gln | Ser | Val | Leu | Asp | Asp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| | | | | | | | | | | | | | | | |
| Phe | Tyr | Thr | Ala | Thr | Glu | Gly | Gln | Tyr | Gln | Gln | Gln | Pro | | | |
| | | | 20 | | | | | 25 | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 74:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Glu | Asp | Arg | Pro | Thr | Phe | Asp | Tyr | Leu | Arg | Ser | Val | Leu | Glu | Asp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| | | | | | | | | | | | | | | | |
| Phe | Phe | Thr | Ala | Thr | Glu | Gly | Gln | Tyr | Gln | Pro | Gln | Pro | | | |
| | | | 20 | | | | | 25 | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 6 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

| | | | | | |
|-----|-----|-----|-----|-----|-----|
| Pro | Xaa | Xaa | Xaa | Xaa | Pro |
| 1 | | | | 5 | |

(2) INFORMATION FOR SEQ ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Asp | Phe | Arg | Leu | Pro | Glu | Ile | Ala | Ile | Pro | Glu | Phe | Ile | Ile | Pro |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| | | | | | | | | | | | | | | | |
| Thr | Leu | Asn | Leu | Asn | Asp | Phe | Gln | Val | Pro | Asp | Leu | His | Ile | Pro | Glu |
| | | | 20 | | | | | 25 | | | | | 30 | | |

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Phe Gln Leu Pro His Ile Ser His
 35 40

(2) INFORMATION FOR SEQ ID NO: 77:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

Pro Gln Asn Ala Lys Leu Lys Ile Lys Arg Pro Val Lys Val Gln Pro
 1 5 10 15

Ile Ala Arg Val Trp Tyr
 20

(2) INFORMATION FOR SEQ ID NO: 78:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

Pro Asp Phe Arg Leu Pro Glu Ile Ala Ile Pro Glu Phe Ile Ile Pro
 1 5 10 15

Thr Leu Asn Leu Asn Asp
 20

(2) INFORMATION FOR SEQ ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

Asn Asp Phe Gln Val Pro Asp Leu His Ile Pro Glu Phe Gln Leu Pro
 1 5 10 15

His Ile Ser His Thr Ile
 20

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(2) INFORMATION FOR SEQ ID NO: 80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

```

Pro Ser Leu Glu Leu Pro Val Leu His Val Pro Arg Asn Leu Lys Leu
1           5           10           15
Ser Leu Pro His Phe Lys
                20

```

(2) INFORMATION FOR SEQ ID NO: 81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 379 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

```

Met Ala Ser Gly Arg Ala Arg Cys Thr Arg Lys Leu Arg Asn Trp Val
1           5           10           15
Val Glu Gln Val Glu Ser Gly Gln Phe Pro Gly Val Cys Trp Asp Asp
                20           25           30
Thr Ala Lys Thr Met Phe Arg Ile Pro Trp Lys His Ala Gly Lys Gln
                35           40           45
Asp Phe Arg Glu Ser Gln Asp Ala Ala Phe Phe Lys Ala Trp Ala Ile
                50           55           60
Phe Lys Gly Lys Tyr Lys Glu Gly Asp Lys Glu Val Pro Glu Arg Gly
65           70           75           80
Arg Met Asp Val Ala Glu Pro Tyr Lys Val Tyr Gln Leu Leu Pro Pro
                85           90           95
Gly Ile Val Ser Gly Gln Pro Gly Thr Gln Lys Val Pro Ser Lys Arg
                100          105          110
Gln His Ser Ser Val Ser Ser Glu Arg Lys Glu Glu Asp Ala Met Gln
                115          120          125
Asn Cys Thr Leu Ser Pro Ser Val Leu Gln Asp Ser Leu Asn Asn Glu
                130          135          140
Glu Gly Ala Ser Gly Gly Ala Val His Ser Asp Ile Gly Ser Ser Ser
145          150          155          160

```

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Ser Ser Ser Ser Pro Glu Pro Gln Glu Val Thr Asp Thr Thr Glu Ala
 165 170 175
 Pro Phe Gln Gly Asp Gln Arg Ser Leu Glu Phe Leu Leu Pro Pro Glu
 180 185 190
 Pro Asp Tyr Ser Leu Leu Leu Thr Phe Ile Tyr Asn Gly Arg Val Val
 195 200 205
 Gly Glu Ala Gln Val Gln Ser Leu Asp Cys Arg Leu Val Ala Glu Pro
 210 215 220
 Ser Gly Ser Glu Ser Ser Met Glu Gln Val Leu Phe Pro Lys Pro Gly
 225 230 235 240
 Pro Glu Pro Thr Gln Arg Leu Leu Ser Gln Leu Glu Arg Gly Ile Leu
 245 250 255
 Val Ala Ser Asn Pro Arg Gly Leu Phe Val Gln Arg Leu Cys Pro Ile
 260 265 270
 Pro Ile Ser Trp Asn Ala Pro Gln Ala Pro Pro Gly Pro Gly Pro His
 275 280 285
 Leu Leu Pro Ser Asn Glu Cys Val Glu Leu Phe Arg Thr Ala Tyr Phe
 290 295 300
 Cys Arg Asp Leu Val Arg Tyr Phe Gln Gly Leu Gly Pro Pro Pro Lys
 305 310 315 320
 Phe Gln Val Thr Leu Asn Phe Trp Glu Glu Ser His Gly Ser Ser His
 325 330 335
 Thr Pro Gln Asn Leu Ile Thr Val Lys Met Glu Gln Ala Phe Ala Arg
 340 345 350
 Tyr Leu Lys Met Glu Gln Ala Phe Ala Arg Tyr Leu Leu Glu Gln Thr
 355 360 365
 Pro Glu Gln Gln Ala Ala Ile Leu Ser Leu Val
 370 375

(2) INFORMATION FOR SEQ ID NO: 82:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 383 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

Val Ser Leu Val Cys Pro Lys Asp Ala Thr Arg Phe Lys His Leu Arg
 1 5 10 15

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Lys Tyr Thr Tyr Asn Tyr Glu Ala Glu Ser Ser Ser Gly Val Pro Gly
 20 25 30
 Thr Ala Asp Ser Arg Ser Ala Thr Arg Ile Asn Cys Lys Val Glu Leu
 35 40 45
 Glu Val Pro Gln Leu Cys Ser Phe Ile Leu Lys Thr Ser Gln Cys Thr
 50 55 60
 Leu Lys Glu Val Tyr Gly Phe Asn Pro Glu Gly Lys Ala Leu Leu Lys
 65 70 75 80
 Lys Thr Lys Asn Ser Glu Glu Phe Ala Ala Ala Met Ser Arg Tyr Glu
 85 90 95
 Leu Lys Leu Ala Ile Pro Glu Gly Lys Gln Val Phe Leu Tyr Pro Glu
 100 105 110
 Lys Asp Glu Pro Thr Tyr Ile Leu Asn Ile Lys Arg Gly Ile Ile Ser
 115 120 125
 Ala Leu Leu Val Pro Pro Glu Thr Glu Glu Ala Lys Gln Val Leu Phe
 130 135 140
 Leu Asp Thr Val Tyr Gly Asn Cys Ser Thr His Phe Thr Val Lys Thr
 145 150 155 160
 Arg Lys Gly Asn Val Ala Thr Glu Ile Ser Thr Glu Arg Asp Leu Gly
 165 170 175
 Gln Cys Asp Arg Phe Lys Pro Ile Arg Thr Gly Ile Ser Pro Leu Ala
 180 185 190
 Leu Ile Lys Gly Met Thr Arg Pro Leu Ser Thr Leu Ile Ser Ser Ser
 195 200 205
 Gln Ser Cys Gln Tyr Thr Leu Asp Ala Lys Arg Lys His Val Ala Glu
 210 215 220
 Ala Ile Cys Lys Glu Gln His Leu Phe Leu Pro Phe Ser Tyr Lys Asn
 225 230 235 240
 Lys Tyr Gly Met Val Ala Gln Val Thr Gln Thr Leu Lys Leu Glu Asp
 245 250 255
 Thr Pro Lys Ile Asn Ser Arg Phe Phe Gly Glu Gly Thr Lys Lys Met
 260 265 270
 Gly Leu Ala Phe Glu Ser Thr Lys Ser Thr Ser Pro Pro Lys Gln Ala
 275 280 285
 Glu Ala Val Leu Lys Thr Leu Gln Glu Leu Lys Lys Leu Thr Ile Ser
 290 295 300

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Glu Gln Asn Ile Gln Arg Ala Asn Leu Phe Asn Lys Leu Val Thr Glu
 305 310 315 320
 Leu Arg Gly Leu Ser Asp Glu Ala Val Thr Ser Leu Leu Pro Gln Leu
 325 330 335
 Ile Glu Val Ser Ser Pro Ile Thr Leu Gln Ala Leu Val Gln Cys Gly
 340 345 350
 Gln Pro Gln Cys Ser Thr His Ile Leu Lys Arg Val His Ala Asn Pro
 355 360 365
 Leu Leu Ile Asp Val Val Thr Tyr Leu Val Ala Leu Ile Pro Glu
 370 375 380

(2) INFORMATION FOR SEQ ID NO: 83:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 394 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

Phe Gly Leu Ser Asn Lys Ile Asn Ser Lys His Leu Arg Val Asn Gln
 1 5 10 15
 Asn Leu Val Tyr Glu Ser Gly Ser Leu Asn Phe Ser Lys Leu Glu Ile
 20 25 30
 Gln Ser Gln Val Asp Ser Gln His Val Gly His Ser Val Leu Thr Ala
 35 40 45
 Lys Gly Met Ala Leu Phe Gly Glu Gly Lys Ala Glu Phe Thr Gly Arg
 50 55 60
 His Asp Ala His Leu Asn Gly Lys Val Ile Gly Thr Leu Lys Asn Ser
 65 70 75 80
 Leu Phe Phe Ser Ala Gln Pro Phe Glu Ile Thr Ala Ser Thr Asn Asn
 85 90 95
 Glu Gly Asn Leu Lys Val Arg Phe Pro Leu Arg Leu Thr Gly Lys Ile
 100 105 110
 Asp Phe Leu Asn Asn Tyr Ala Leu Phe Leu Ser Pro Ser Ala Gln Gln
 115 120 125
 Ala Ser Trp Gln Val Ser Ala Arg Phe Asn Gln Tyr Lys Tyr Asn Gln
 130 135 140
 Asn Phe Ser Ala Gly Asn Asn Glu Asn Ile Met Glu Ala His Val Gly
 145 150 155 160

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```

Ile Asn Gly Glu Ala Asn Leu Asp Phe Leu Asn Ile Pro Leu Thr Ile
      165                                170                                175

Pro Glu Met Arg Leu Pro Tyr Thr Ile Ile Thr Thr Pro Pro Leu Lys
      180                                185                                190

Asp Phe Ser Leu Trp Glu Lys Thr Gly Leu Lys Glu Phe Leu Lys Thr
      195                                200                                205

Thr Lys Gln Ser Phe Asp Leu Ser Val Lys Ala Gln Tyr Lys Lys Asn
      210                                215                                220

Lys His Arg His Ser Ile Asn Pro Leu Ala Val Leu Cys Glu Phe Ile
      225                                230                                235                                240

Ser Gln Ser Ile Lys Ser Phe Asp Arg His Phe Glu Lys Asn Arg Asn
      245                                250                                255

Asn Ala Leu Asp Phe Val Thr Lys Ser Tyr Asn Glu Thr Lys Ile Lys
      260                                265                                270

Phe Asp Lys Tyr Lys Ala Glu Lys Ser His Asp Glu Leu Pro Arg Thr
      275                                280                                285

Phe Gln Ile Pro Gly Tyr Thr Val Pro Val Val Asn Val Glu Val Ser
      290                                295                                300

Pro Phe Thr Ile Glu Met Ser Ala Phe Gly Tyr Val Phe Pro Lys Ala
      305                                310                                315                                320

Val Ser Met Pro Ser Phe Ser Ile Leu Gly Ser Asp Val Arg Val Pro
      325                                330                                335

Ser Tyr Thr Leu Ile Leu Pro Ser Leu Glu Leu Pro Val Leu His Val
      340                                345                                350

Pro Arg Asn Leu Lys Leu Ser Leu Pro His Phe Lys Glu Leu Cys Thr
      355                                360                                365

Ile Ser His Ile Phe Ile Pro Ala Met Gly Asn Ile Thr Tyr Asp Phe
      370                                375                                380

Ser Phe Lys Ser Ser Val Ile Thr Leu Asn
      385                                390

```

(2) INFORMATION FOR SEQ ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

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Met Ala Ser Gly Arg Ala Arg Cys Thr Arg Lys Leu Arg Asn Trp Val
 1 5 10 15

Val Glu Gln Val Glu Ser Gly Gln Phe Pro Gly Val Cys Trp Asp Asp
 20 25 30

Thr Ala Lys Thr Met Phe Arg Ile Pro Trp Lys His Ala Gly Lys Gln
 35 40 45

Asp Phe Arg
 50

(2) INFORMATION FOR SEQ ID NO: 85:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

Pro Lys Asp Ala Thr Arg Phe Lys His Leu Arg Lys Tyr Thr Tyr Asn
 1 5 10 15

Tyr Glu Ala Glu Ser Ser Ser Gly Val Pro Gly Thr Ala Asp Ser Arg
 20 25 30

Ser Ala Thr Arg Ile Asn Cys Lys Val Glu Leu Glu Val Leu Pro Gln
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

Pro Glu Gly Lys Ala Leu Leu Lys Lys Thr Lys Asn Ser Glu Glu Phe
 1 5 10 15

Ala Ala Ala Met Ser Arg Tyr Glu Leu Lys Leu Ala Ile Pro Glu Gly
 20 25 30

Lys Gln Val Phe Leu
 35

(2) INFORMATION FOR SEQ ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

```

Cys Ser Thr His Phe Thr Val Lys Thr Arg Lys Gly Asn Val Ala Thr
1           5           10           15
Glu Ile Ser Thr Glu Arg Asp Leu Gly Gln Cys Asp Arg Phe Lys Pro
          20           25           30
Ile Arg Thr Gly Ile Ser
          35

```

(2) INFORMATION FOR SEQ ID NO: 88:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 51 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

```

Cys Ser Thr His Ile Leu Gln Trp Leu Lys Arg Val His Ala Asn Pro
1           5           10           15
Leu Leu Ile Asp Val Val Thr Tyr Leu Val Ala Leu Ile Pro Glu Pro
          20           25           30
Ser Ala Gln Gln Leu Arg Glu Ile Phe Asn Met Ala Arg Asp Gln Arg
          35           40           45
Ser Arg Ala
          50

```

(2) INFORMATION FOR SEQ ID NO: 89:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 38 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

```

His Leu Ser Cys Asp Thr Lys Glu Glu Arg Lys Ile Lys Gly Val Ile
1           5           10           15
Ser Ile Pro Arg Leu Gln Ala Glu Ala Arg Ser Glu Ile Leu Ala His
          20           25           30

```

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Trp Ser Pro Ala Lys Leu
35

(2) INFORMATION FOR SEQ ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 47 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Val | His | Leu | Asp | Ser | Lys | Lys | Lys | Gln | His | Leu | Phe | Val | Lys | Glu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Val | Lys | Ile | Asp | Gly | Gln | Phe | Arg | Val | Ser | Ser | Phe | Tyr | Ala | Lys | Gly |
| | | | 20 | | | | | 25 | | | | | | 30 | |
| Thr | Tyr | Gly | Leu | Ser | Cys | Gln | Arg | Asp | Pro | Asn | Thr | Gly | Arg | Leu | |
| | | 35 | | | | | 40 | | | | | 45 | | | |

(2) INFORMATION FOR SEQ ID NO: 91:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | His | Ile | Asn | Ile | Asp | Gln | Phe | Val | Arg | Lys | Tyr | Arg | Ala | Ala | Leu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Gly | Lys | Leu | Pro | Gln | Gln | Ala | Asn | Asp | Tyr | Leu | Ser | Phe | Asn | Trp | Glu |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Arg | Gln | Val | Ser | His | Ala | Lys | Glu | | | | | | | | |
| | | 35 | | | | | 40 | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Leu | Thr | Ala | Leu | Thr | Lys | Lys | Tyr | Arg | Ile | Thr | Glu | Asn | Asp | Ile |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

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Gln Ile Ala Leu Asp Asp Ala Lys Ile Asn Phe Asn Glu Lys Leu Ser
 20 25 30

Gln Leu Gln Thr Tyr Met Ile Gln
 35 40

(2) INFORMATION FOR SEQ ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 50 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

Glu Arg Ile Asn Asp Val Leu Glu His Val Lys His Phe Val Ile Asn
 1 5 10 15

Leu Ile Gly Asp Phe Glu Val Ala Glu Lys Ile Asn Ala Phe Arg Ala
 20 25 30

Lys Val His Glu Leu Ile Glu Arg Tyr Glu Val Asp Gln Gln Ile Gln
 35 40 45

Val Leu
 50

(2) INFORMATION FOR SEQ ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 50 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

Asn Lys Phe Leu Asp Met Leu Ile Lys Lys Leu Lys Ser Phe Asp Tyr
 1 5 10 15

His Gln Phe Val Asp Glu Thr Asn Asp Lys Ile Arg Glu Val Thr Gln
 20 25 30

Arg Leu Asn Gly Glu Ile Gln Ala Leu Glu Leu Pro Gln Lys Ala Glu
 35 40 45

Ala Leu
 50

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(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 23 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

```

Ser Asn Lys Ile Asn Ser Lys His Leu Arg Val Asn Gln Asn Leu Val
1           5           10           15

Tyr Glu Ser Gly Ser Leu Asn
                20

```

(2) INFORMATION FOR SEQ ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 47 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

```

Phe Ser Lys Leu Glu Ile Gln Ser Gln Val Asp Ser Gln His Val Gly
1           5           10           15

His Ser Val Leu Thr Ala Lys Gly Met Ala Leu Phe Gly Glu Gly Gly
                20           25           30

Lys Ala Glu Phe Thr Gly Arg His Asp Ala His Leu Asn Gly Lys
                35           40           45

```

(2) INFORMATION FOR SEQ ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 50 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

```

Val Lys Ala Gln Tyr Lys Lys Asn Lys His Arg His Ser Ile Thr Asn
1           5           10           15

Pro Leu Ala Val Leu Cys Glu Phe Ile Ser Gln Ser Ile Lys Ser Phe
                20           25           30

Asp Arg His Phe Glu Lys Asn Arg Asn Asn Ala Leu Asp Phe Val Thr
                35           40           45

```

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Lys Ser
50

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys Arg Gly Leu Lys Leu
1 5 10 15

Ala Thr Ala Leu Ser Leu Ser Asn Lys Phe Val Glu Gly Ser His Asn
20 25 30

Ser Thr Val Ser Leu Thr Thr Lys Asn Met Glu Val Ser Val Ala Lys
35 40 45

Thr Thr Lys
50

(2) INFORMATION FOR SEQ ID NO: 99:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

Lys Leu Asp Val Thr Thr Ser Ile Gly Arg Arg Gln His Leu Arg Val
1 5 10 15

Ser Thr Ala Phe Val Tyr Thr Lys Asn Pro Asn Gly Tyr Ser Phe Ser
20 25 30

Ile Pro Val Lys Val Leu Ala Asp Lys Phe Ile Thr Pro Gly Leu Lys
35 40 45

Leu Asn Asp
50

(2) INFORMATION FOR SEQ ID NO: 100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 49 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

```

Phe Arg Glu Ile Gln Ile Tyr Lys Lys Leu Arg Thr Ser Ser Phe Ala
1           5           10           15
Leu Asn Leu Pro Thr Leu Pro Glu Val Lys Phe Pro Glu Val Asp Val
          20           25           30
Leu Thr Lys Tyr Ser Gln Pro Glu Asp Ser Leu Ile Pro Phe Phe Glu
          35           40           45
Ile

```

(2) INFORMATION FOR SEQ ID NO: 101:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

```

Leu His Leu Arg Tyr Gln Lys Asp Lys Lys Gly Ile Ser Thr Ser Ala
1           5           10           15
Ala Ser Pro Ala Val Gly Thr Val Gly Met Asp Met Asp Glu Asp Asp
          20           25           30
Asp Phe Ser Lys Trp Asn Phe Tyr Tyr Ser Pro Gln Ser Ser Pro Asp
          35           40           45

```

(2) INFORMATION FOR SEQ ID NO: 102:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

```

Leu Arg Glu Val Ser Ser Lys Leu Arg Arg Asn Leu Gln Asn Asn Ala
1           5           10           15
Glu Trp Val Tyr Gln Gly Ala Ile Arg Gln Ile Asp Asp Ile Asp Val
          20           25           30
Arg Phe Gln Lys Ala Ala Ser Gly Thr Thr Gly Thr Tyr Gln Glu Trp
          35           40           45

```

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(2) INFORMATION FOR SEQ ID NO: 103:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 50 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

```

Arg Val Thr Gln Lys Phe His Met Lys Val Lys His Leu Ile Asp Ser
1              5              10              15
Leu Ile Asp Phe Leu Asn Phe Pro Arg Phe Gln Phe Pro Gly Lys Pro
              20              25              30
Gly Ile Tyr Thr Arg Glu Glu Leu Cys Thr Met Phe Ile Arg Glu Val
              35              40              45
Gly Thr
              50

```

(2) INFORMATION FOR SEQ ID NO: 104:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

```

Trp Lys His Ala Gly Lys Gln Asp Phe Arg Glu Ser Gln Asp Ala Ala
1              5              10              15
Phe Phe Lys Ala Trp Ala Ile Phe Lys Gly Lys Tyr Lys Glu Gly Asp
              20              25              30
Lys Glu Val Pro Glu Arg Gly Arg Met Asp Val Ala Glu Pro Tyr Lys
              35              40              45

```

(2) INFORMATION FOR SEQ ID NO: 105:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 48 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

```

Glu His Val Lys His Phe Val Ile Asn Leu Ile Gly Asp Phe Glu Val
1              5              10              15

```

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Ala Glu Lys Ile Asn Ala Phe Arg Ala Lys Val His Glu Leu Ile Glu
 20 25 30

Arg Tyr Glu Val Asp Gln Gln Ile Gln Val Leu Met Asp Lys Leu Val
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 106:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 52 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

Val Arg Lys Tyr Arg Ala Ala Leu Gly Lys Leu Pro Gln Gln Ala Asn
 1 5 10 15

Asp Tyr Leu Asn Ser Phe Asn Trp Glu Arg Gln Val Ser His Ala Lys
 20 25 30

Glu Lys Leu Thr Ala Leu Thr Lys Lys Tyr Arg Ile Thr Glu Asn Asp
 35 40 45

Ile Gln Ile Ala
 50

(2) INFORMATION FOR SEQ ID NO: 107:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 57 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

Tyr Ile Lys Asp Ser Tyr Asp Leu His Asp Leu Lys Ile Ala Ile Ala
 1 5 10 15

Asn Ile Ile Asp Glu Ile Ile Glu Lys Leu Lys Ser Leu Asp Glu His
 20 25 30

Tyr His Ile Arg Val Asn Leu Val Lys Thr Ile His Asp Leu His Leu
 35 40 45

Phe Ile Glu Asn Ile Asp Phe Asn Lys
 50 55

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(2) INFORMATION FOR SEQ ID NO: 108:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

```

Lys Ile Thr Leu Ile Ile Asn Trp Leu Gln Glu Ala Leu Ser Ser Ala
1           5           10           15
Ser Leu Ala His Met Lys Ala Lys Phe Arg Glu Thr Leu Glu Asp Thr
          20           25           30
Arg

```

(2) INFORMATION FOR SEQ ID NO: 109:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:

```

Thr Asp His Phe Ser Leu Arg Ala Arg Tyr His Met Lys Ala Asp Ser
1           5           10           15
Val Val Asp Leu Ser Tyr Asn Val Gln Gly Ser Gly Glu Thr Thr Tyr
          20           25           30

```

(2) INFORMATION FOR SEQ ID NO: 110:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:

```

Lys Leu Thr Thr Asn Gly Arg Phe Arg Glu His Asn Ala Lys Phe Ser
1           5           10           15
Leu Asp Gly Lys
          20

```

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(2) INFORMATION FOR SEQ ID NO: 111:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 52 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

```

Asp Thr Lys Tyr Gln Ile Arg Ile Gln Ile Gln Glu Lys Leu Gln Gln
1           5           10           15
Leu Lys Arg His Ile Gln Asn Ile Asp Ile Gln His Leu Ala Gly Lys
          20           25           30
Leu Lys Gln His Ile Glu Ala Ile Asp Val Arg Val Leu Leu Asp Gln
          35           40           45
Leu Gly Thr Thr
          50

```

(2) INFORMATION FOR SEQ ID NO: 112:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:

```

Phe His Asp Phe Pro Asp Leu Gly Gln Glu Val Ala Leu Asn Ala Asn
1           5           10           15
Thr Lys Asn Gln Lys Ile Arg Trp Lys Asn Glu Val Arg Ile His Ser
          20           25           30
Gly Ser Phe Gln Ser Gln Val Glu Leu Ser Asn Asp Gln
          35           40           45

```

(2) INFORMATION FOR SEQ ID NO: 113:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:

```

Lys Asp Asn Val Phe Asp Gly Leu Val Arg Val Thr Gln Lys Phe His
1           5           10           15

```

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Met Lys Val Lys His Leu Ile Asp Ser Leu Ile Asp Phe Leu Asn Phe
 20 25 30

Pro Arg

(2) INFORMATION FOR SEQ ID NO: 114:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 35 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:

His Arg Asn Ile Gln Glu Tyr Leu Ser Ile Leu Thr Asp Pro Asp Gly
 1 5 10 15

Lys Gly Lys Glu Lys Ile Ala Glu Leu Ser Ala Thr Ala Gln Glu Ile
 20 25 30

Ile Lys Ser
 35

(2) INFORMATION FOR SEQ ID NO: 115:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 211 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

Glu Phe Thr Ile Val Ala Phe Val Lys Tyr Asp Lys Asn Gln Asp Val
 1 5 10 15

His Ser Ile Asn Leu Pro Phe Phe Glu Thr Leu Gln Glu Tyr Phe Glu
 20 25 30

Arg Asn Arg Gln Thr Ile Ile Val Val Leu Glu Asn Val Gln Arg Lys
 35 40 45

Leu Lys His Ile Asn Ile Asp Gln Phe Val Arg Lys Tyr Arg Ala Ala
 50 55 60

Leu Gly Lys Leu Pro Gln Gln Ala Asn Asp Tyr Leu Asn Ser Phe Asn
 65 70 75 80

Trp Glu Arg Gln Val Ser His Ala Lys Glu Lys Leu Thr Ala Leu Thr
 85 90 95

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```

Lys Lys Tyr Arg Ile Thr Glu Asn Asp Ile Gln Ile Ala Leu Asp Asp
      100                      105                      110

Ala Lys Ile Asn Phe Asn Glu Lys Leu Ser Gln Leu Gln Thr Tyr Met
      115                      120                      125

Ile Gln Phe Asp Gln Tyr Ile Lys Asp Ser Tyr Asp Leu His Asp Leu
      130                      135                      140

Lys Ile Ala Ile Ala Asn Ile Ile Asp Glu Ile Ile Glu Lys Leu Lys
      145                      150                      155                      160

Ser Leu Asp Glu His Tyr His Ile Arg Val Ile Leu Val Lys Thr Ile
      165                      170                      175

His Asp Leu His Leu Phe Ile Glu Asn Ile Asp Phe Asn Lys Ser Gly
      180                      185                      190

Ser Ser Thr Ala Ser Trp Ile Gln Asn Val Asp Thr Lys Tyr Gln Ile
      195                      200                      205

Arg Ile Gln
      210

```

(2) INFORMATION FOR SEQ ID NO: 116:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 174 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

```

Gly Pro Leu Pro Thr Leu Val Ser Gly Gly Thr Ile Leu Ala Thr Val
1              5              10              15

Pro Leu Val Val Asp Ala Glu Lys Leu Pro Ile Asn Arg Leu Ala Ala
      20              25              30

Gly Ser Lys Ala Pro Ala Ser Ala Gln Ser Arg Gly Glu Lys Arg Thr
      35              40              45

Ala His Asn Ala Ile Glu Lys Arg Tyr Arg Ser Ser Ile Asn Asp Lys
      50              55              60

Ile Ile Glu Leu Lys Asp Leu Val Val Gly Thr Glu Ala Lys Leu Asn
      65              70              75              80

Lys Ser Ala Val Leu Arg Lys Ala Ile Asp Tyr Ile Arg Phe Leu Gln
      85              90              95

His Ser Asn Gln Lys Leu Lys Gln Glu Asn Leu Ser Leu Arg Thr Ala
      100             105             110

```

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Val His Lys Ser Lys Ser Leu Lys Asp Leu Val Ser Ala Cys Gly Ser
 115 120 125

Gly Gly Asn Thr Asp Val Leu Met Glu Gly Val Lys Thr Glu Val Glu
 130 135 140

Asp Thr Leu Thr Pro Pro Pro Ser Asp Ala Gly Ser Pro Phe Gln Ser
 145 150 155 160

Ser Pro Leu Ser Leu Gly Ser Arg Gly Ser Gly Ser Gly Gly
 165 170

(2) INFORMATION FOR SEQ ID NO: 117:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 172 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

Gln Val Pro Thr Leu Val Gly Ser Ser Gly Thr Ile Leu Thr Thr Met
 1 5 10 15

Pro Val Met Met Gly Gln Glu Lys Val Pro Ile Lys Gln Val Pro Gly
 20 25 30

Gly Val Lys Gln Leu Glu Pro Pro Lys Glu Gly Glu Arg Arg Thr Thr
 35 40 45

His Asn Ile Ile Glu Lys Arg Tyr Arg Ser Ser Ile Asn Asp Lys Ile
 50 55 60

Ile Glu Leu Lys Asp Leu Val Met Gly Thr Asp Ala Lys Met His Lys
 65 70 75 80

Ser Gly Val Leu Arg Lys Ala Ile Asp Tyr Ile Lys Tyr Leu Gln Gln
 85 90 95

Val Asn His Lys Leu Arg Gln Glu Asn Met Val Leu Lys Leu Ala Asn
 100 105 110

Gln Lys Asn Lys Leu Leu Lys Gly Ile Asp Leu Gly Ser Leu Val Asp
 115 120 125

Asn Glu Val Asp Leu Lys Ile Glu Asp Phe Asn Gln Asn Val Leu Leu
 130 135 140

Met Ser Pro Pro Ala Ser Asp Ser Gly Ser Gln Ala Gly Phe Ser Pro
 145 150 155 160

Tyr Ser Ile Asp Ser Glu Pro Gly Ser Pro Leu Leu
 165 170

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(2) INFORMATION FOR SEQ ID NO: 118:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 173 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:

| | | | | | | | | | | | | | | | |
|---------|---------|---------|---------|---------|-----|---------|--------|---------|--------|---------|--------|--------|---------|---------|---------|
| Gly 1 | Pro | Leu | Gln | Thr 5 | Leu | Val | Ser | Gly | Gly 10 | Thr | Ile | Leu | Ala | Thr 15 | Val |
| Pro | Leu | Val | Val 20 | Asp | Thr | Asp | Lys | Leu 25 | Pro | Ile | His | Arg | Leu 30 | Ala | Ala |
| Gly | Gly | Lys 35 | Ala | Leu | Gly | Ser | Ala 40 | Gln | Ser | Arg | Gly | Glu 45 | Lys | Arg | Thr |
| Ala | His 50 | Asn | Ala | Ile | Glu | Lys 55 | Arg | Tyr | Arg | Ser | Ser 60 | Ile | Asn | Asp | Lys |
| Ile 65 | Val | Glu | Leu | Lys 70 | Asp | Leu | Val | Val | Gly | Thr 75 | Glu | Ala | Lys | Leu 80 | Asn |
| Lys | Ser | Ala | Val 85 | Leu | Arg | Lys | Ala | Ile 90 | Asp | Tyr | Ile | Arg | Phe | Leu 95 | Gln |
| His | Ser | Asn 100 | Gln | Lys | Leu | Lys | Gln | Glu 105 | Asn | Leu | Thr | Leu | Arg | Ser 110 | Ala |
| His | Lys 115 | Ser | Lys | Ser | Leu | Lys | Asp | Leu 120 | Val | Ser | Ala | Cys | Gly 125 | Ser | Gly |
| Gly 130 | Gly | Thr | Asp | Val | Ser | Met 135 | Glu | Gly | Met | Lys | Pro | Glu | Val | Val | Glu |
| Thr 145 | Leu | Thr | Pro | Pro 150 | Pro | Ser | Asp | Ala | Gly | Ser 155 | Pro | Ser | Gln | Ser | Ser 160 |
| Pro | Leu | Ser | Leu 165 | Gly | Ser | Arg | Gly | Ser 170 | Ser | Ser | Gly | Gly | | | |

(2) INFORMATION FOR SEQ ID NO: 119:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 243 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Glu | Pro | Pro | Gln | Ser | Pro | Trp | Asp | Arg | Val | Lys | Asp | Leu | Ala | Thr | 1 | 5 | 10 | 15 |
| Val | Tyr | Val | Asp | Val | Leu | Lys | Asp | Ser | Gly | Arg | Asp | Tyr | Val | Ser | Gln | 20 | 25 | 30 | |
| Phe | Glu | Gly | Ser | Ala | Leu | Gly | Lys | Gln | Leu | Asn | Leu | Lys | Leu | Leu | Asp | 35 | 40 | 45 | |
| Asn | Trp | Asp | Ser | Val | Thr | Ser | Thr | Phe | Ser | Lys | Leu | Arg | Glu | Gln | Leu | 50 | 55 | 60 | |
| Gly | Pro | Val | Thr | Gln | Glu | Phe | Trp | Asp | Asn | Leu | Glu | Lys | Glu | Thr | Glu | 65 | 70 | 75 | 80 |
| Gly | Leu | Arg | Gln | Glu | Met | Ser | Lys | Asp | Leu | Glu | Glu | Val | Lys | Ala | Lys | 85 | 90 | 95 | |
| Val | Gln | Pro | Tyr | Leu | Asp | Asp | Phe | Gln | Lys | Lys | Trp | Gln | Glu | Glu | Met | 100 | 105 | 110 | |
| Glu | Leu | Tyr | Arg | Gln | Lys | Val | Glu | Pro | Leu | Arg | Ala | Glu | Leu | Gln | Glu | 115 | 120 | 125 | |
| Gly | Ala | Arg | Gln | Lys | Leu | His | Glu | Leu | Gln | Glu | Lys | Leu | Ser | Pro | Leu | 130 | 135 | 140 | |
| Gly | Glu | Glu | Met | Arg | Asp | Arg | Ala | Arg | Ala | His | Val | Asp | Ala | Leu | Arg | 145 | 150 | 155 | 160 |
| Thr | His | Leu | Ala | Pro | Tyr | Ser | Asp | Glu | Leu | Arg | Gln | Arg | Leu | Ala | Ala | 165 | 170 | 175 | |
| Arg | Leu | Glu | Ala | Leu | Lys | Glu | Asn | Gly | Gly | Ala | Arg | Leu | Ala | Glu | Tyr | 180 | 185 | 190 | |
| His | Ala | Lys | Ala | Thr | Glu | His | Leu | Ser | Thr | Leu | Ser | Glu | Lys | Ala | Lys | 195 | 200 | 205 | |
| Pro | Ala | Leu | Glu | Asp | Leu | Arg | Gln | Gly | Leu | Leu | Pro | Val | Leu | Glu | Ser | 210 | 215 | 220 | |
| Phe | Lys | Val | Ser | Phe | Leu | Ser | Ala | Leu | Glu | Glu | Tyr | Thr | Lys | Lys | Leu | 225 | 230 | 235 | 240 |
| Asn | Thr | Gln | | | | | | | | | | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 120:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 268 amino acids

(B) TYPE: amino acid

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(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Gln | Val | Pro | Val | Leu | Leu | Gln | Pro | His | Phe | Ile | Lys | Ala | Asp | Ser | 1 | 5 | 10 | 15 |
| Leu | Leu | Leu | Thr | Ala | Met | Lys | Thr | Asp | Gly | Ala | Thr | Val | Lys | Ala | Ala | 20 | 25 | 30 | |
| Gly | Leu | Ser | Pro | Leu | Val | Ser | Gly | Thr | Thr | Val | Gln | Thr | Gly | Pro | Leu | 35 | 40 | 45 | |
| Pro | Thr | Leu | Val | Ser | Gly | Gly | Thr | Ile | Leu | Ala | Thr | Val | Pro | Leu | Val | 50 | 55 | 60 | |
| Val | Asp | Ala | Glu | Lys | Leu | Pro | Ile | Asn | Arg | Leu | Ala | Ala | Gly | Ser | Lys | 65 | 70 | 75 | 80 |
| Ala | Pro | Ala | Ser | Ala | Gln | Ser | Arg | Gly | Glu | Lys | Arg | Thr | Ala | His | Asn | 85 | 90 | 95 | |
| Ala | Ile | Glu | Lys | Arg | Tyr | Arg | Ser | Ser | Ile | Asn | Asp | Lys | Ile | Ile | Glu | 100 | 105 | 110 | |
| Leu | Lys | Asp | Leu | Val | Val | Gly | Thr | Glu | Ala | Lys | Leu | Asn | Lys | Ser | Ala | 115 | 120 | 125 | |
| Val | Leu | Arg | Lys | Ala | Ile | Asp | Tyr | Ile | Arg | Phe | Leu | Gln | His | Ser | Asn | 130 | 135 | 140 | |
| Gln | Lys | Leu | Lys | Gln | Glu | Asn | Leu | Ser | Leu | Arg | Thr | Ala | Val | His | Lys | 145 | 150 | 155 | 160 |
| Ser | Lys | Ser | Leu | Lys | Asp | Leu | Val | Ser | Ala | Cys | Gly | Ser | Gly | Gly | Asn | 165 | 170 | 175 | |
| Thr | Asp | Val | Leu | Met | Glu | Gly | Val | Lys | Thr | Glu | Val | Glu | Asp | Thr | Leu | 180 | 185 | 190 | |
| Thr | Pro | Pro | Pro | Ser | Asp | Ala | Gly | Ser | Pro | Phe | Gln | Ser | Ser | Pro | Leu | 195 | 200 | 205 | |
| Ser | Leu | Gly | Ser | Arg | Gly | Ser | Gly | Ser | Gly | Gly | Ser | Gly | Ser | Asp | Ser | 210 | 215 | 220 | |
| Glu | Pro | Asp | Ser | Pro | Val | Phe | Glu | Asp | Ser | Lys | Ala | Lys | Pro | Glu | Gln | 225 | 230 | 235 | 240 |
| Arg | Pro | Ser | Leu | His | Ser | Arg | Gly | Met | Leu | Asp | Arg | Ser | Arg | Leu | Ala | 245 | 250 | 255 | |
| Leu | Cys | Thr | Leu | Val | Phe | Leu | Cys | Leu | Ser | Cys | Asn | 260 | 265 | | | | | | |

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(2) INFORMATION FOR SEQ ID NO: 121:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 77 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

```

Gln Ala Lys Glu Pro Cys Val Glu Ser Leu Val Ser Gln Tyr Phe Gln
1              5              10              15
Thr Val Thr Asp Tyr Gly Lys Asp Leu Met Glu Lys Val Lys Ser Pro
              20              25              30
Glu Leu Gln Ala Glu Ala Lys Ser Tyr Phe Glu Lys Ser Lys Glu Gln
              35              40              45
Leu Thr Pro Leu Ile Lys Lys Ala Gly Thr Glu Leu Val Asn Phe Leu
              50              55              60
Ser Tyr Phe Val Glu Leu Gly Thr Gln Pro Ala Thr Gln
65              70              75

```

(2) INFORMATION FOR SEQ ID NO: 122:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 71 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

```

Glu Ala Lys Leu Asn Lys Ser Ala Val Leu Arg Lys Ala Ile Asp Tyr
1              5              10              15
Ile Arg Phe Leu Gln His Ser Asn Gln Lys Leu Lys Gln Glu Asn Leu
              20              25              30
Ser Leu Arg Thr Ala Val His Lys Ser Lys Ser Leu Lys Asp Leu Val
              35              40              45
Ser Ala Cys Gly Ser Gly Gly Asn Thr Asp Val Leu Met Glu Gly Val
              50              55              60
Lys Thr Glu Val Glu Asp Thr
65              70

```

(2) INFORMATION FOR SEQ ID NO: 123:

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 397 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:

| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Lys | Ser | Glu | Leu | Thr | Gln | Gln | Leu | Asn | Ala | Leu | Phe | Gln | Asp | Lys | 1 | 5 | 10 | 15 |
| Leu | Gly | Glu | Val | Asn | Thr | Tyr | Ala | Gly | Asp | Leu | Gln | Lys | Lys | Leu | Val | 20 | 25 | 30 | |
| Pro | Phe | Ala | Thr | Glu | Leu | His | Glu | Arg | Leu | Ala | Lys | Asp | Ser | Glu | Lys | 35 | 40 | 45 | |
| Leu | Lys | Glu | Glu | Ile | Gly | Lys | Glu | Leu | Glu | Glu | Leu | Arg | Ala | Arg | Leu | 50 | 55 | 60 | |
| Leu | Pro | His | Ala | Asn | Glu | Val | Ser | Gln | Lys | Ile | Gly | Asp | Asn | Leu | Arg | 65 | 70 | 75 | 80 |
| Glu | Leu | Gln | Gln | Arg | Leu | Glu | Pro | Tyr | Ala | Asp | Gln | Leu | Arg | Thr | Gln | 85 | 90 | 95 | |
| Val | Asn | Thr | Gln | Ala | Glu | Gln | Leu | Arg | Arg | Gln | Leu | Asp | Pro | Leu | Ala | 100 | 105 | 110 | |
| Gln | Arg | Met | Glu | Arg | Val | Leu | Arg | Glu | Asn | Ala | Asp | Ser | Leu | Gln | Ala | 115 | 120 | 125 | |
| Ser | Leu | Arg | Pro | His | Ala | Asp | Glu | Leu | Lys | Ala | Lys | Ile | Asp | Gln | Asn | 130 | 135 | 140 | |
| Val | Glu | Glu | Leu | Lys | Gly | Arg | Leu | Thr | Pro | Tyr | Ala | Asp | Glu | Phe | Lys | 145 | 150 | 155 | 160 |
| Val | Lys | Ile | Asp | Gln | Thr | Val | Glu | Glu | Leu | Arg | Arg | Ser | Leu | Ala | Pro | 165 | 170 | 175 | |
| Tyr | Ala | Gln | Asp | Thr | Gln | Glu | Lys | Leu | Asn | His | Gln | Leu | Glu | Gly | Leu | 180 | 185 | 190 | |
| Thr | Phe | Gln | Met | Lys | Lys | Asn | Ala | Glu | Glu | Leu | Lys | Ala | Arg | Ile | Ser | 195 | 200 | 205 | |
| Ala | Ser | Ala | Glu | Ile | Asp | Gln | Thr | Val | Glu | Glu | Leu | Arg | Arg | Ser | Leu | 210 | 215 | 220 | |
| Ala | Pro | Tyr | Ala | Gln | Asp | Thr | Gln | Glu | Lys | Leu | Asn | His | Gln | Leu | Glu | 225 | 230 | 235 | 240 |
| Gly | Leu | Thr | Phe | Gln | Met | Lys | Lys | Asn | Ala | Glu | Glu | Leu | Lys | Ala | Arg | 245 | 250 | 255 | |

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Ile Ser Ala Ser Ala Glu Glu Leu Arg Gln Arg Leu Ala Pro Leu Ala
260 265 270

Glu Asp Val Arg Gly Asn Leu Lys Gly Asn Thr Glu Gly Leu Gln Lys
275 280 285

Ser Leu Ala Glu Leu Gly Gly His Leu Asp Gln Gln Val Glu Glu Phe
290 295 300

Arg Arg Arg Val Glu Pro Tyr Gly Glu Asn Phe Asn Lys Ala Leu Val
305 310 315 320

Gln Gln Met Glu Gln Leu Arg Gln Lys Leu Gly Pro His Ala Gly Asp
325 330 335

Val Glu Gly His Leu Ser Phe Leu Glu Lys Asp Leu Arg Asp Lys Val
340 345 350

Asn Ser Phe Phe Ser Thr Phe Lys Glu Lys Glu Ser Gln Asp Lys Thr
355 360 365

Leu Ser Leu Pro Glu Leu Glu Gln Gln Gln Glu Gln Gln Glu Gln
370 375 380

Gln Gln Glu Gln Val Gln Met Leu Ala Pro Leu Glu Ser
385 390 395

(2) INFORMATION FOR SEQ ID NO: 124:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 422 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

Glu Lys Leu Pro Ile Asn Arg Leu Ala Ala Gly Ser Lys Ala Pro Ala
1 5 10 15

Ser Ala Gln Ser Arg Gly Glu Lys Arg Thr Ala His Asn Ala Ile Glu
20 25 30

Lys Arg Tyr Arg Ser Ser Ile Asn Asp Lys Ile Ile Glu Leu Lys Asp
35 40 45

Leu Val Val Gly Thr Glu Ala Lys Leu Asn Lys Ser Ala Val Leu Arg
50 55 60

Lys Ala Ile Asp Tyr Ile Arg Phe Leu Gln His Ser Asn Gln Lys Leu
65 70 75 80

Lys Gln Glu Asn Leu Ser Leu Arg Thr Ala Val His Lys Ser Lys Ser
85 90 95

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Lys | Asp | Leu | Val | Ser | Ala | Cys | Gly | Ser | Gly | Gly | Asn | Thr | Asp | Val | 100 | 105 | 110 | |
| Leu | Met | Glu | Gly | Val | Lys | Thr | Glu | Val | Glu | Asp | Thr | Leu | Thr | Pro | Pro | 115 | 120 | 125 | |
| Pro | Arg | Asp | Ala | Gly | Ser | Pro | Phe | Gln | Ser | Ser | Pro | Leu | Ser | Leu | Gly | 130 | 135 | 140 | |
| Ser | Arg | Gly | Ser | Gly | Ser | Gly | Gly | Ser | Gly | Ser | Asp | Ser | Glu | Pro | Asp | 145 | 150 | 155 | 160 |
| Ser | Pro | Val | Phe | Glu | Asp | Ser | Lys | Ala | Lys | Pro | Glu | Gln | Arg | Pro | Ser | 165 | 170 | 175 | |
| Leu | His | Ser | Arg | Gly | Met | Leu | Asp | Arg | Ser | Arg | Leu | Ala | Leu | Cys | Thr | 180 | 185 | 190 | |
| Leu | Val | Phe | Leu | Cys | Leu | Ser | Cys | Asn | Pro | Leu | Ala | Ser | Leu | Leu | Gly | 195 | 200 | 205 | |
| Ala | Arg | Gly | Leu | Pro | Ser | Pro | Ser | Asp | Thr | Thr | Ser | Val | Tyr | His | Ser | 210 | 215 | 220 | |
| Pro | Gly | Arg | Asn | Val | Leu | Gly | Thr | Glu | Ser | Arg | Asp | Gly | Pro | Gly | Trp | 225 | 230 | 235 | 240 |
| Ala | Gln | Ala | Val | Gln | Leu | Phe | Leu | Cys | Asp | Leu | Leu | Leu | Val | Val | Arg | 245 | 250 | 255 | |
| Thr | Ser | Leu | Trp | Arg | Gln | Gln | Gln | Pro | Pro | Ala | Pro | Ala | Pro | Ala | Ala | 260 | 265 | 270 | |
| Gln | Gly | Ala | Ser | Ser | Arg | Pro | Gln | Ala | Ser | Ala | Leu | Glu | Ile | Arg | Gly | 275 | 280 | 285 | |
| Phe | Gln | Arg | Asp | Leu | Ser | Ser | Leu | Arg | Arg | Leu | Ala | Gln | Ser | Phe | Arg | 290 | 295 | 300 | |
| Pro | Ala | Met | Arg | Arg | Val | Phe | Leu | His | Glu | Ala | Thr | Ala | Arg | Leu | Met | 305 | 310 | 315 | 320 |
| Ala | Gly | Ala | Ser | Pro | Thr | Arg | Thr | His | Gln | Leu | Leu | Asp | Arg | Ser | Leu | 325 | 330 | 335 | |
| Arg | Arg | Arg | Ala | Gly | Pro | Gly | Gly | Lys | Gly | Gly | Ala | Val | Ala | Glu | Leu | 340 | 345 | 350 | |
| Glu | Pro | Arg | Pro | Thr | Arg | Arg | Glu | His | Ala | Glu | Ala | Leu | Leu | Leu | Ala | 355 | 360 | 365 | |
| Ser | Cys | Tyr | Leu | Pro | Pro | Gly | Phe | Leu | Ser | Ala | Pro | Gly | Gln | Arg | Val | 370 | 375 | 380 | |
| Gly | Met | Leu | Ala | Glu | Ala | Ala | Arg | Thr | Leu | Glu | Lys | Leu | Gly | Asp | Arg | 385 | 390 | 395 | 400 |

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Arg Leu Leu His Asp Cys Gln Gln Met Leu Met Arg Leu Gly Gly Gly
 405 410 415

Thr Thr Val Thr Ser Ser
 420

(2) INFORMATION FOR SEQ ID NO: 125:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 142 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 125:

Glu Lys Met Ser Leu Arg Asn Arg Leu Ser Lys Ser Arg Glu Asn Pro
 1 5 10 15

Glu Glu Asp Glu Asp Gln Arg Asn Pro Ala Lys Glu Ser Leu Glu Thr
 20 25 30

Pro Ser Asn Gly Arg Ile Asp Ile Lys Gln Leu Ile Ala Lys Lys Ile
 35 40 45

Lys Leu Thr Ala Asn Gly Arg Ile Asp Ile Lys Gln Leu Ile Ala Lys
 50 55 60

Lys Ile Lys Leu Thr Ala Glu Asn Gly Arg Ile Asp Ile Lys Gln Leu
 65 70 75 80

Ile Ala Lys Lys Ile Lys Leu Thr Ala Glu Ala Glu Glu Leu Lys Pro
 85 90 95

Phe Phe Met Lys Glu Val Gly Ser His Phe Asp Asp Phe Val Thr Asn
 100 105 110

Leu Ile Glu Lys Ser Ala Ser Leu Asp Asn Lys Ala His Ser Phe Val
 115 120 125

Arg Glu Asn Val Pro Arg Val Leu Asn Ser Ala Lys Glu Lys
 130 135 140

(2) INFORMATION FOR SEQ ID NO: 126:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 135 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:

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Glu Lys Leu Pro Ile Asn Arg Leu Ala Ala Gly Ser Lys Ala Pro Ala
 1 5 10 15
 Ser Ala Gln Ser Arg Gly Glu Lys Arg Thr Ala His Asn Ala Ile Glu
 20 25 30
 Lys Arg Tyr Arg Ser Ser Ile Asn Asp Lys Ile Ile Glu Leu Lys Asp
 35 40 45
 Leu Val Val Gly Thr Glu Ala Lys Leu Asn Lys Ser Tyr Ile Arg Phe
 50 55 60
 Leu Gln His Ser Asn Gln Lys Leu Lys Gln Glu Asn Leu Ser Leu Arg
 65 70 75 80
 Thr Ala Val His Lys Ser Lys Ser Leu Lys Asp Leu Val Ser Ala Cys
 85 90 95
 Gly Ser Gly Gly Asn Thr Asp Val Leu Met Glu Gly Val Lys Thr Glu
 100 105 110
 Val Glu Asp Lys Ala Lys Pro Glu Gln Arg Pro Ser Leu His Ser Arg
 115 120 125
 Gly Met Leu Asp Arg Ser Arg
 130 135

(2) INFORMATION FOR SEQ ID NO: 127:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 26 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:

Arg Arg His Cys Pro Leu Lys Asn Pro Thr Phe Leu Asp Tyr Val Arg
 1 5 10 15
 Pro Arg Ser Trp Thr Cys Arg Tyr Val Phe
 20 25

(2) INFORMATION FOR SEQ ID NO: 128:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 25 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:

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Arg Arg Arg Ala Gly Pro Gly Gly Lys Gly Gly Ala Val Ala Glu Leu
 1 5 10 15

Glu Pro Arg Pro Thr Arg Arg Glu His
 20 25

(2) INFORMATION FOR SEQ ID NO: 129:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 114 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:

Ala Met Leu Gly Gln Ser Thr Glu Glu Leu Arg Val Arg Leu Ala Ser
 1 5 10 15

His Leu Arg Lys Leu Arg Lys Arg Leu Leu Arg Asp Ala Asp Asp Leu
 20 25 30

Gln Lys Arg Leu Ala Val Tyr Gln Ala Gly Ala Arg Glu Gly Ala Glu
 35 40 45

Arg Gly Leu Ser Ala Ile Arg Glu Arg Leu Gly Pro Leu Val Glu Gln
 50 55 60

Gly Arg Val Arg Ala Ala Thr Val Gly Ser Leu Ala Gly Gln Pro Leu
 65 70 75 80

Gln Glu Arg Ala Gln Ala Trp Gly Glu Arg Leu Arg Ala Arg Met Glu
 85 90 95

Glu Met Gly Ser Arg Thr Arg Asp Arg Leu Asp Glu Val Lys Glu Gln
 100 105 110

Val Ala

(2) INFORMATION FOR SEQ ID NO: 130:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 107 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:

Lys Leu Pro Ile Asn Arg Leu Ala Ala Gly Ser Lys Ala Pro Ala Ser
 1 5 10 15

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Gln | Ser | Arg | Gly | Glu | Lys | Arg | Thr | Ala | His | Asn | Ala | Ile | Glu | Lys |
| | | | 20 | | | | 25 | | | | | | 30 | | |
| Arg | Tyr | Arg | Ser | Ser | Ile | Asn | Asp | Lys | Ile | Ile | Glu | Leu | Lys | Asp | Leu |
| | | | 35 | | | | 40 | | | | 45 | | | | |
| Val | Val | Gly | Thr | Glu | Ala | Lys | Leu | Asn | Lys | Ser | Ala | Val | Leu | Arg | Lys |
| | | | 50 | | | | 55 | | | | 60 | | | | |
| Ala | Ile | Asp | Tyr | Ile | Arg | Phe | Leu | Gln | His | Ser | Asn | Gln | Lys | Leu | Lys |
| 65 | | | | | | 70 | | | | 75 | | | 80 | | |
| Gln | Glu | Asn | Leu | Ser | Leu | Arg | Thr | Ala | Val | His | Lys | Ser | Lys | Ser | Leu |
| | | | 85 | | | | | | 90 | | | 95 | | | |
| Lys | Asp | Leu | Val | Ser | Ala | Cys | Gly | Ser | Gly | Gly | | | | | |
| | | | 100 | | | 105 | | | | | | | | | |

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

Thr Gln Gln Pro Gln Gln Asp Glu Met Pro Ser Pro Thr Phe Leu Thr
1 5 10 15
Gln Val Lys Glu Ser Leu Ser Ser Tyr Trp Glu Ser Ala Lys Thr Ala
20 25 30
Ala Gln Asn Leu Tyr Glu Lys Thr Tyr Leu
35 40

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gln | Ile | Gln | Gln | Val | Pro | Val | Leu | Leu | Gln | Pro | His | Phe | Ile | Lys |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Ala | Asp | Ser | Leu | Leu | Leu | Thr | Ala | Met | Lys | Thr | Asp | Gly | Ala | Thr | Val |
| | | | 20 | | | | | 25 | | | | | 30 | | |

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Lys Ala Ala Gly Leu Ser Pro Leu Val Ser Gly Thr Thr
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 133:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133:

Ser Leu Leu Ser Phe Met Gln Gly Tyr Met Lys His Ala Thr Lys Thr
 1 5 10 15

Ala Lys Asp Ala Leu Ser Ser Val Gln Glu Ser Gln Val Ala Gln Gln
 20 25 30

Ala Arg Gly Trp Val Thr Asp Gly Phe Ser Ser Leu Lys
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 134:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 47 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 134:

Ala Pro Ala Ser Ala Gln Ser Arg Gly Glu Lys Arg Thr Ala His Asn
 1 5 10 15

Ala Ile Glu Lys Arg Tyr Arg Ser Ser Ile Asn Asp Lys Ile Ile Glu
 20 25 30

Leu Lys Asp Leu Val Val Gly Thr Glu Ala Lys Leu Asn Lys Ser
 35 40 45

(2) INFORMATION FOR SEQ ID NO: 135:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:

Asp Tyr Trp Ser Thr Val Lys Asp Lys Phe Ser Glu Phe Trp Asp Leu
 1 5 10 15

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Asp Pro Glu Val Arg Pro Thr Ser Ala Val Ala Ala
20 25

(2) INFORMATION FOR SEQ ID NO: 136:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 136:

Glu Ile Tyr Val Ala Ala Ala Leu Arg Val Lys Thr Ser Leu Pro Arg
1 5 10 15
Ala Leu His Phe Leu Thr Arg Phe Phe Leu Ser Ser Ala Arg Gln Ala
20 25 30

(2) INFORMATION FOR SEQ ID NO: 137:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:

Glu Lys Ile Pro Thr
1 5

(2) INFORMATION FOR SEQ ID NO: 138:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 5 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:

Glu Lys Leu Pro Ile
1 5

(2) INFORMATION FOR SEQ ID NO: 139:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Asn | Gly | Arg | Cys | Ile | Gln | Ala | Asn | Tyr | Ser | Leu | Met | Glu | Asn | Gly |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| | | | | | | | | | | | | | | | |
| Lys | Ile | Lys | Val | Leu | Asn | Gln | Glu | Leu | Arg | Ala | Asp | Gly | | | |
| | | | 20 | | | | | 25 | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 140:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Val | Leu | Arg | Lys | Ala | Ile | Asp | Tyr | Ile | Arg | Phe | Leu | Gln | His | Ser |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| | | | | | | | | | | | | | | | |
| Asn | Gln | Lys | Leu | Lys | Gln | Glu | Asn | Leu | Ser | Leu | Arg | Thr | Ala | Val | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 141:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Lys | Gln | Leu | Glu | Asp | Lys | Val | Glu | Glu | Leu | Leu | Ser | Lys | Asn | Tyr |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| | | | | | | | | | | | | | | | |
| His | Leu | Glu | Asn | Glu | Val | Ala | Arg | Leu | Lys | Lys | Leu | Val | Gly | Glu | Arg |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 142:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:

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- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 144:

```

Arg Ile Gln Ile Gln Glu Lys Leu Gln Gln Leu Lys Arg His Ile Gln
1           5           10          15
Asn Ile Asp Ile Gln His Leu Ala Gly Lys Leu Lys Gln His Ile Glu
          20          25          30

```

(2) INFORMATION FOR SEQ ID NO: 145:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 35 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 145:

```

Val Leu Gln Gln Val Lys Ile Lys Asp Tyr Phe Glu Lys Leu Val Gly
1           5           10          15
Phe Ile Asp Asp Ala Val Lys Lys Leu Asn Glu Leu Ser Phe Lys Thr
          20          25          30
Phe Ile Glu
          35

```

(2) INFORMATION FOR SEQ ID NO: 146:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 31 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 146:

```

Glu Leu Ser Phe Lys Thr Phe Ile Glu Asp Val Asn Lys Phe Leu Asp
1           5           10          15
Met Leu Ile Lys Lys Leu Lys Ser Phe Asp Tyr His Gln Phe Val
          20          25          30

```

(2) INFORMATION FOR SEQ ID NO: 147:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 28 amino acids
 - (B) TYPE: amino acid

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- (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 147:

His Gln Phe Val Asp Glu Thr Asn Asp Lys Ile Arg Glu Val Thr Gln
 1 5 10 15

Arg Leu Asn Gly Glu Ile Gln Ala Leu Glu Leu Pro
 20 25

(2) INFORMATION FOR SEQ ID NO: 148:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 31 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 148:

Ala Ala Lys Asn Leu Thr Asp Phe Ala Glu Gln Tyr Ser Ile Gln Asp
 1 5 10 15

Trp Ala Lys Arg Met Lys Ala Leu Val Glu Gln Gly Phe Thr Val
 20 25 30

(2) INFORMATION FOR SEQ ID NO: 149:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 35 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:

Ser Ala Ser Leu Ala His Met Lys Ala Lys Phe Arg Glu Thr Leu Glu
 1 5 10 15

Asp Thr Arg Asp Arg Met Tyr Asp Met Asp Ile Gln Gln Glu Leu Gln
 20 25 30

Arg Tyr Leu
 35

(2) INFORMATION FOR SEQ ID NO: 150:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 35 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

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(2) INFORMATION FOR SEQ ID NO: 149:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 35 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 149:

```

Ser Ala Ser Leu Ala His Met Lys Ala Lys Phe Arg Glu Thr Leu Glu
1           5           10           15
Asp Thr Arg Asp Arg Met Tyr Asp Met Asp Ile Gln Gln Glu Leu Gln
          20           25           30
Arg Tyr Leu
          35

```

(2) INFORMATION FOR SEQ ID NO: 150:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 35 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 150:

```

Cys Leu Asn Leu His Lys Phe Asn Glu Phe Ile Gln Asn Glu Leu Gln
1           5           10           15
Glu Ala Ser Gln Glu Leu Gln Gln Ile His Gln Tyr Ile Met Ala Leu
          20           25           30
Arg Glu Glu
          35

```

(2) INFORMATION FOR SEQ ID NO: 151:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 151:

```

Phe Leu Ile Tyr Ile Thr Glu Leu Leu Lys Lys Leu Gln Ser Thr Thr
1           5           10           15
Val Met Asn Pro Tyr Met Lys Leu Ala Pro Gly Glu Leu Thr Ile Ile
          20           25           30

```

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(2) INFORMATION FOR SEQ ID NO: 152:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 152:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Leu | Leu | Asp | His | Arg | Val | Pro | Glu | Thr | Asp | Met | Thr | Phe | Arg | His |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Val | Gly | Ser | Lys | Leu | Ile | Val | Ala | Met | Ser | Ser | Trp | Leu | Gln | | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 153:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 153:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Asn | Phe | Ser | Lys | Leu | Glu | Ile | Gln | Ser | Gln | Val | Asp | Ser | Gln | His |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Val | Gly | His | Ser | Val | Leu | Thr | Ala | Lys | Gly | Met | Ala | Leu | Phe | | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 154:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 154:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Gln | Asn | Phe | Ser | Ala | Gly | Asn | Asn | Glu | Asn | Ile | Met | Glu | Ala | His |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Val | Gly | Ile | Asn | Gly | Glu | Ala | Asn | Leu | Asp | Phe | Leu | Asn | Ile | | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

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(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 155:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Val | Val | Thr | Arg | Ile | Ala | Pro | Ser | Pro | Thr | Gly | Asp | Pro | His | Val |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| | | | | | | | | | | | | | | | |
| Gly | Thr | Ala | Tyr | Ile | Ala | Leu | Phe | Asn | Tyr | Ala | Trp | Ala | | | |
| | | | 20 | | | | | 25 | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 156:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 156:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Thr | Val | His | Thr | Arg | Phe | Pro | Pro | Glu | Pro | Asn | Gly | Tyr | Leu | His |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| | | | | | | | | | | | | | | | |
| Ile | Gly | His | Ala | Lys | Ser | Ile | Cys | Leu | Asn | Phe | Gly | Ile | Ala | | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 157:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 157:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Ile | Lys | Leu | Tyr | Cys | Gly | Val | Asp | Pro | Thr | Ala | Gln | Ser | Leu | His |
| 1 | | | 5 | | | | | | 10 | | | | | 15 | |
| | | | | | | | | | | | | | | | |
| Leu | Gly | Asn | Leu | Val | Pro | Met | Val | Leu | Leu | His | Phe | Tyr | Val | | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 158:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:

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(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 158:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Ile | Ala | Leu | Tyr | Cys | Gly | Phe | Asp | Pro | Thr | Ala | Asp | Ser | Leu | His |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Leu | Gly | His | Leu | Val | Pro | Leu | Leu | Cys | Leu | Lys | Arg | Gly | Gln | | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 159:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 159:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Val | Thr | Leu | Tyr | Cys | Gly | Phe | Asp | Pro | Thr | Ala | Asp | Ser | Leu | His |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Ile | Gly | Asn | Leu | Ala | Ala | Ile | Leu | Thr | Leu | Arg | Arg | Phe | Gln | | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 160:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 160:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ile | Gly | Ala | Tyr | Val | Gly | Ile | Asp | Pro | Thr | Ala | Pro | Ser | Leu | His |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Val | Gly | His | Leu | Leu | Pro | Leu | Met | Pro | Leu | Phe | Trp | Met | Tyr | | |
| | | | 20 | | | | | 25 | | | | | 30 | | |

(2) INFORMATION FOR SEQ ID NO: 161:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 161:

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Pro Ile Ala Leu Tyr Cys Gly Phe Asp Pro Thr Ala Asp Ser Leu His
 1 5 10 15
 Leu Gly His Leu Val Pro Leu Leu Cys Leu Lys Arg Phe Gln
 20 25 30

(2) INFORMATION FOR SEQ ID NO: 162:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 162:

Pro Leu Lys Val Lys Leu Gly Ala Asp Pro Thr Ala Pro Asp Ile His
 1 5 10 15
 Leu Gly His Thr Val Val Leu Asn Lys Leu Arg Gln Phe Gln
 20 25 30

(2) INFORMATION FOR SEQ ID NO: 163:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 163:

Val Ser Lys Gly Leu Leu Ile Phe Asp Ala Ser Ser Ser Met Gly Pro
 1 5 10 15
 Gln Met Ser Ala Ser Val His Leu Asp Ser Lys Lys Lys Gln His Leu
 20 25 30
 Phe Val Lys Glu Val Lys Ile Asp Gly Gln Phe
 35 40

(2) INFORMATION FOR SEQ ID NO: 164:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 164:

Thr Ile Ile Thr Thr Pro Pro Leu Lys Asp Phe Ser Leu Trp Glu Lys
 1 5 10 15

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Thr Gly Leu Lys Glu Phe Leu Lys Thr Thr Lys Gln Ser Phe Asp Leu
 20 25 30

Ser Val Lys Ala Gln Tyr Lys Lys Asn Lys His
 35 40

(2) INFORMATION FOR SEQ ID NO: 165:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 165:

Lys Asn Arg Asn Asn Ala Leu Asp Phe Val Thr Lys Ser Tyr Asn Glu
 1 5 10 15

Thr Lys Ile Lys Phe Asp Lys Tyr Lys Ala Glu Lys Ser Gln Asp Glu
 20 25 30

Leu Pro Arg Thr Phe Gln Ile
 35

(2) INFORMATION FOR SEQ ID NO: 166:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 166:

Asp Ala Leu Gln Tyr Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys
 1 5 10 15

Arg Gly Leu Lys Leu Ala Thr Ala Leu Ser Leu Ser Asn Lys Phe Val
 20 25 30

Glu Gly Ser His
 35

(2) INFORMATION FOR SEQ ID NO: 167:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 167:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ala | Phe | Gly | Trp | Glu | Ala | Pro | Arg | Glu | Tyr | His | Met | Pro | Leu | Leu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Arg | Asn | Pro | Asp | Lys | Thr | Lys | Ile | Ser | Lys | Arg | Lys | Ser | His | Thr | Ser |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Leu | Asp | Trp | Tyr | Lys | Ala | Glu | Gly | Phe | Leu | | | | | | |
| | | 35 | | | | | 40 | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 168:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 168:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Asn | Ile | Thr | Ile | Pro | Val | His | Pro | Arg | Gln | Tyr | Glu | Phe | Ser | Arg |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Leu | Asn | Leu | Glu | Tyr | Thr | Val | Met | Ser | Lys | Arg | Lys | Leu | Asn | Leu | Leu |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Val | Thr | Asp | Lys | His | Val | Glu | Gly | Trp | Asp | | | | | | |
| | | 35 | | | | | 40 | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 169:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 169:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Asn | Lys | Gly | Leu | Pro | Phe | Gly | Ile | Thr | Val | Pro | Leu | Leu | Thr | Thr |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Ala | Thr | Gly | Glu | Lys | Phe | Gly | Lys | Ser | Ala | Gly | Asn | Ala | Val | Phe | Ile |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Asp | Pro | Ser | Ile | Asn | Thr | Ala | Tyr | | | | | | | | |
| | | 35 | | | | | 40 | | | | | | | | |

(2) INFORMATION FOR SEQ ID NO: 170:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 41 amino acids

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- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 170:

```

Arg Leu His Gln Asn Gln Val Phe Gly Leu Thr Val Pro Leu Ile Thr
1           5           10           15
Lys Ala Asp Gly Thr Lys Phe Gly Lys Thr Glu Gly Gly Ala Val Trp
          20           25           30
Leu Asp Pro Lys Lys Thr Ser Pro Tyr
          35           40

```

(2) INFORMATION FOR SEQ ID NO: 171:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 42 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 171:

```

Lys Thr Lys Gly Glu Ala Arg Ala Phe Gly Leu Thr Ile Pro Leu Val
1           5           10           15
Thr Lys Ala Asp Gly Thr Lys Phe Gly Lys Thr Glu Ser Gly Thr Ile
          20           25           30
Trp Leu Asp Lys Glu Lys Thr Ser Pro Tyr
          35           40

```

(2) INFORMATION FOR SEQ ID NO: 172:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 41 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 172:

```

Lys Thr Ala Leu Asp Glu Cys Val Gly Phe Thr Val Pro Leu Leu Thr
1           5           10           15
Asp Ser Ser Gly Ala Lys Phe Gly Lys Ser Ala Gly Asn Ala Ile Trp
          20           25           30
Leu Asp Pro Tyr Gln Thr Ser Val Phe
          35           40

```

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(2) INFORMATION FOR SEQ ID NO: 173:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 41 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 173:

```

Arg Leu His Gln Asn Gln Val Phe Gly Leu Thr Val Pro Leu Ile Thr
1              5              10              15

Lys Ala Asp Gly Thr Lys Phe Gly Lys Thr Glu Gly Gly Ala Val Trp
              20              25              30

Leu Asp Pro Lys Lys Thr Ser Pro Tyr
              35              40

```

(2) INFORMATION FOR SEQ ID NO: 174:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 174:

```

Ser Ala Gly Lys Lys Pro Gln Val Ala Ile Thr Leu Pro Leu Leu Val
1              5              10              15

Gly Leu Asp Gly Glu Lys Lys Met Ser Lys Ser Leu Gly Asn Tyr Ile
              20              25              30

Gly Val Thr Glu Ala Pro Ser Asp Met Phe
              35              40

```

(2) INFORMATION FOR SEQ ID NO: 175:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 35 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 175:

```

Arg Val Ser Thr Ala Phe Val Tyr Thr Lys Asn Pro Asn Gly Tyr Ser
1              5              10              15

Phe Ser Ile Pro Val Lys Val Leu Ala Asp Lys Phe Ile Thr Pro Gly
              20              25              30

```

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Leu Lys Leu
35

(2) INFORMATION FOR SEQ ID NO: 176:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 176:

Lys Leu Gly Gln Gly Cys Phe Gly Glu Val Trp Met Gly Thr Trp Asn
1 5 10 15

Gly Thr Thr Arg Val Ala Ile Lys Thr Leu Lys Pro Gly
20 25

(2) INFORMATION FOR SEQ ID NO: 177:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 177:

His Ile Gly His
1

(2) INFORMATION FOR SEQ ID NO: 178:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 178:

His Lys Asn Thr Ser Thr Leu Ser Cys Asp Gly Ser Leu Arg His Lys
1 5 10 15

Phe

(2) INFORMATION FOR SEQ ID NO: 179:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids

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- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 179:

Arg Lys Leu Lys His Ile Asn Ile Asp Gln Phe Val Arg Lys Tyr Arg
1 5 10 15
Ala

(2) INFORMATION FOR SEQ ID NO: 180:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 180:

Arg His Ile Gln Asn Ile Asp Ile Gln His Leu Ala Gly Lys Leu Lys
1 5 10 15
Gln His

(2) INFORMATION FOR SEQ ID NO: 181:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 181:

Lys Lys Gly Phe Tyr Lys Lys Lys Gln Cys Arg Pro Ser Lys Gly Arg
1 5 10 15
Lys

(2) INFORMATION FOR SEQ ID NO: 182:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 182:

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Lys Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Gln Ile Arg Gly Arg
1 5 10 15

Glu Arg

(2) INFORMATION FOR SEQ ID NO: 183:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 183:

Lys Arg Ala Leu Pro Asn Asn Thr Ser Ser Ser Pro Gln Pro Lys Lys
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 184:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 184:

Lys Lys Thr Asn Leu Phe Ser Ala Leu Ile Lys Lys Lys Lys Lys Thr
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO: 185:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 185:

Arg Lys Thr Leu Leu Asn Ser Leu Glu Glu Ala Lys Lys Lys Lys Glu
1 5 10 15

Asp

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(2) INFORMATION FOR SEQ ID NO: 186:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 186:

Arg Arg Glu Leu Asp Glu Ser Leu Gln Val Ala Glu Arg Leu Thr Arg
1 5 10 15
Lys

(2) INFORMATION FOR SEQ ID NO: 187:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 187:

Arg Arg Ser Tyr Ala Leu Val Ser Leu Ser Phe Phe Arg Lys Leu Arg
1 5 10 15
Leu

(2) INFORMATION FOR SEQ ID NO: 188:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 188:

Arg Arg Tyr Gly Asp Glu Glu Leu His Leu Cys Val Ser Arg Lys His
1 5 10 15
Phe

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(2) INFORMATION FOR SEQ ID NO: 189:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 189:

Lys Arg Val Ala Lys Arg Lys Leu Ile Glu Gln Asn Arg Glu Arg Arg
1 5 10 15

Arg

(2) INFORMATION FOR SEQ ID NO: 190:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 190:

His Arg Ser Thr Asn Ala Gln Gly Ser His Trp Lys Gln Arg Arg Lys
1 5 10 15

Phe

(2) INFORMATION FOR SEQ ID NO: 191:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 191:

Lys Arg Pro Pro Ile Ser Asp Ser Glu Glu Leu Ser Ala Lys Lys Arg
1 5 10 15

Lys

(2) INFORMATION FOR SEQ ID NO: 192:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 amino acids
 (B) TYPE: amino acid

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- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 192:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Lys | Gly | Lys | Lys | Pro | Lys | Thr | Glu | Lys | Glu | Asp | Lys | Val | Lys | His |
| 1 | | | | 5 | | | | | 10 | | | | 15 | | |

Ile

(2) INFORMATION FOR SEQ ID NO: 193:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 17 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 193:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Lys | Arg | Met | Arg | Asn | Arg | Ile | Ala | Ala | Ser | Lys | Cys | Arg | Lys | Arg |
| 1 | | | 5 | | | | | | 10 | | | | | 15 | |

Lys

(2) INFORMATION FOR SEQ ID NO: 194:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 194:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | His | Ile | Gln | Asn | Ile | Asp | Ile | Gln | His | Leu | Ala | Gly | Lys | Leu | Lys |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

Gln His

(2) INFORMATION FOR SEQ ID NO: 195:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 21 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 195:

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Lys Lys Ile Thr Glu Val Ala Leu Met Gly His Leu Ser Cys Asp Thr
1 5 10 15

Lys Glu Glu Arg Lys
20

(2) INFORMATION FOR SEQ ID NO: 196:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 196:

Lys His Ile Asn Ile Asp Gln Phe Val Arg Lys Tyr Arg Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO: 197:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 197:

His Arg Asn Ile Gln Glu Tyr Leu Ser Ile Leu Thr Asp Pro Asp Gly
1 5 10 15

Lys Gly Lys Glu Lys
20

(2) INFORMATION FOR SEQ ID NO: 198:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 198:

Lys Glu Val Tyr Gly Phe Asn Pro Glu Gly Lys Ala Leu Leu Lys Lys
1 5 10 15

Thr Lys

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(2) INFORMATION FOR SEQ ID NO: 199:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 199:

Lys Val Leu Val Asp His Phe Gly Tyr Thr Lys Asp Asp Lys His Glu
1 5 10 15
Asp Met

(2) INFORMATION FOR SEQ ID NO: 200:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 200:

Lys Ala Gly Lys Leu Lys Phe Ile Ile Pro Ser Pro Lys Arg Pro Val
1 5 10 15
Lys Leu

(2) INFORMATION FOR SEQ ID NO: 201:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 201:

Arg Gln Val Ser His Ala Lys Glu Lys Leu Thr Ala Leu Thr Lys Lys
1 5 10 15
Tyr Arg

(2) INFORMATION FOR SEQ ID NO: 202:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 amino acids

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- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 202:

Lys Tyr Gln Ile Arg Ile Gln Ile Gln Glu Lys Leu Gln Gln Leu Lys
1 5 10 15

Arg His

(2) INFORMATION FOR SEQ ID NO: 203:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 20 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 203:

Lys Gly Met Ala Leu Phe Gly Glu Gly Lys Ala Glu Phe Thr Gly Arg
1 5 10 15

His Asp Ala His
 20

(2) INFORMATION FOR SEQ ID NO: 204:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 204:

Lys Gln Ser Phe Asp Leu Ser Val Lys Ala Gln Tyr Lys Lys Asn Lys
1 5 10 15

His Arg

(2) INFORMATION FOR SEQ ID NO: 205:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 205:

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Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys Arg Gly Leu Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 206:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 206:

Lys Leu Asp Val Thr Thr Ser Ile Gly Arg Arg Gln His Leu Arg
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 207:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 207:

Lys Leu Asp Phe Arg Glu Ile Gln Ile Tyr Lys Lys Leu Arg
1 5 10

(2) INFORMATION FOR SEQ ID NO: 208:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 16 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 208:

Lys Ser Pro Ala Thr Asp Leu His Leu Arg Tyr Gln Lys Asp Lys Lys
1 5 10 15

(2) INFORMATION FOR SEQ ID NO: 209:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 209:

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Lys Tyr His Trp Glu His Thr Gly Leu Thr Leu Arg Glu Val Ser Ser
 1 5 10 15

Lys Leu Arg Arg
 20

(2) INFORMATION FOR SEQ ID NO: 210:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 21 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 210:

Lys Asp Asn Val Phe Asp Gly Leu Val Arg Val Thr Gln Lys Phe His
 1 5 10 15

Met Lys Val Lys His
 20

(2) INFORMATION FOR SEQ ID NO: 211:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 180 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 211:

Ser Ile Asn Leu Pro Phe Phe Glu Thr Leu Gln Glu Tyr Phe Glu Arg
 1 5 10 15

Asn Arg Gln Thr Ile Ile Val Val Leu Glu Asn Val Gln Arg Lys Leu
 20 25 30

Lys His Ile Asn Ile Asp Gln Phe Val Arg Lys Tyr Arg Ala Ala Leu
 35 40 45

Gly Lys Leu Pro Gln Gln Ala Asn Asp Tyr Leu Asn Ser Phe Asn Trp
 50 55 60

Glu Arg Gln Val Ser His Ala Lys Glu Lys Leu Thr Ala Leu Thr Lys
 65 70 75 80

Lys Tyr Arg Ile Thr Glu Asn Asp Ile Gln Ile Ala Leu Asp Asp Ala
 85 90 95

Lys Ile Asn Phe Asn Glu Lys Leu Ser Gln Leu Gln Thr Tyr Met Ile
 100 105 110

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Gln Phe Asp Gln Tyr Ile Lys Asp Ser Tyr Asp Leu His Asp Leu Lys
 115 120 125

Ile Ala Ile Ala Asn Ile Ile Asp Glu Ile Ile Glu Lys Leu Lys Ser
 130 135 140

Leu Asp Glu His Tyr His Ile Arg Val Ile Leu Val Lys Thr Ile His
 145 150 155 160

Asp Leu His Leu Phe Ile Glu Asn Ile Asp Phe Asn Lys Ser Gly Ser
 165 170 175

Ser Thr Ala Ser
 180

(2) INFORMATION FOR SEQ ID NO: 212:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 94 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 212:

Pro Gln Gln Val Asn Asp Tyr Leu Ser Thr Phe Ser Trp Glu Arg Gln
 1 5 10 15

Val Leu Ser Ala Lys Lys Lys His Ser Asp Phe Met Glu Asp Tyr Arg
 20 25 30

Ile Thr Glu Asn Asp Val Arg Ile Ala Leu Asp Asn Ala Lys Ile Asn
 35 40 45

Leu Asn Glu Lys Leu Thr Gln Leu Gln Thr Tyr Val Ile Gln Phe Asp
 50 55 60

Gln Tyr Ile Lys Asp Asn Tyr Asp Leu His Asp Phe Lys Thr Ala Ile
 65 70 75 80

Ala Arg Ile Ile Asp Glu Ile Ile Ala Thr Leu Lys Ile Leu
 85 90

(2) INFORMATION FOR SEQ ID NO: 213:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 85 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 213:

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Lys Tyr Arg Val Ala Leu Ser Arg Leu Pro Gln Gln Ile His Asp Tyr
 1 5 10 15
 Leu Asn Ala Ser Asp Trp Glu Arg Gln Val Ala Gly Ala Lys Glu Lys
 20 25 30
 Leu Thr Ser Phe Met Glu Asn Tyr Arg Ile Thr Asp Asn Asp Val Leu
 35 40 45
 Ile Ala Leu Asp Ser Ala Lys Ile Asn Leu Asn Glu Lys Leu Ser Gln
 50 55 60
 Leu Glu Thr Tyr Ala Ile Gln Phe Asp Gln Tyr Ile Arg Asp Asn Tyr
 65 70 75 80
 Asp Ala Gln Asp Leu
 85

(2) INFORMATION FOR SEQ ID NO: 214:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 840 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 214:

Leu Asn Asp Phe Gln Val Pro Asp Leu His Ile Pro Glu Phe Gln Leu
 1 5 10 15
 Pro His Ile Ser His Thr Ile Glu Val Pro Thr Phe Gly Lys Leu Tyr
 20 25 30
 Ser Ile Leu Lys Ile Gln Ser Pro Leu Phe Thr Leu Asp Ala Asn Ala
 35 40 45
 Asp Ile Gly Asn Gly Thr Thr Ser Ala Asn Glu Ala Gly Ile Ala Ala
 50 55 60
 Ser Ile Thr Ala Lys Gly Glu Ser Lys Leu Glu Val Leu Asn Phe Asp
 65 70 75 80
 Phe Gln Ala Asn Ala Gln Leu Ser Asn Pro Lys Ile Asn Pro Leu Ala
 85 90 95
 Leu Lys Glu Ser Val Lys Phe Ser Ser Lys Tyr Leu Arg Thr Glu His
 100 105 110
 Gly Ser Glu Met Leu Phe Phe Gly Asn Ala Ile Glu Gly Lys Ser Asn
 115 120 125
 Thr Val Ala Ser Leu His Thr Glu Lys Asn Thr Leu Glu Leu Ser Asn
 130 135 140

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Val | Ile | Val | Lys | Ile | Asn | Asn | Gln | Leu | Thr | Leu | Asp | Ser | Asn | Thr | 145 | 150 | 155 | 160 |
| Lys | Tyr | Phe | His | Lys | Leu | Asn | Ile | Pro | Lys | Leu | Asp | Phe | Ser | Ser | Gln | 165 | 170 | 175 | |
| Ala | Asp | Leu | Arg | Asn | Glu | Ile | Lys | Thr | Leu | Leu | Lys | Ala | Gly | His | Ile | 180 | 185 | 190 | |
| Ala | Trp | Thr | Ser | Ser | Gly | Lys | Gly | Ser | Trp | Lys | Trp | Ala | Cys | Pro | Arg | 195 | 200 | 205 | |
| Phe | Ser | Asp | Glu | Gly | Thr | His | Glu | Ser | Gln | Ile | Ser | Phe | Thr | Ile | Glu | 210 | 215 | 220 | |
| Gly | Pro | Leu | Thr | Ser | Phe | Gly | Leu | Ser | Asn | Lys | Ile | Asn | Ser | Lys | His | 225 | 230 | 235 | 240 |
| Leu | Arg | Val | Asn | Gln | Asn | Leu | Val | Tyr | Glu | Ser | Gly | Ser | Leu | Asn | Phe | 245 | 250 | 255 | |
| Ser | Lys | Leu | Glu | Ile | Gln | Ser | Gln | Val | Asp | Ser | Gln | His | Val | Gly | His | 260 | 265 | 270 | |
| Ser | Val | Leu | Thr | Ala | Lys | Gly | Met | Ala | Leu | Phe | Gly | Glu | Gly | Lys | Ala | 275 | 280 | 285 | |
| Glu | Phe | Thr | Gly | Arg | His | Asp | Ala | His | Leu | Asn | Gly | Lys | Val | Ile | Gly | 290 | 295 | 300 | |
| Thr | Leu | Lys | Asn | Ser | Leu | Phe | Phe | Ser | Ala | Gln | Pro | Phe | Glu | Ile | Thr | 305 | 310 | 315 | 320 |
| Ala | Ser | Thr | Asn | Asn | Glu | Gly | Asn | Leu | Lys | Val | Arg | Phe | Pro | Leu | Arg | 325 | 330 | 335 | |
| Leu | Thr | Gly | Lys | Ile | Asp | Phe | Leu | Asn | Asn | Tyr | Ala | Leu | Phe | Leu | Ser | 340 | 345 | 350 | |
| Pro | Ser | Ala | Gln | Gln | Ala | Ser | Trp | Gln | Val | Ser | Ala | Arg | Phe | Asn | Gln | 355 | 360 | 365 | |
| Tyr | Lys | Tyr | Asn | Gln | Asn | Phe | Ser | Ala | Gly | Asn | Asn | Glu | Asn | Ile | Met | 370 | 375 | 380 | |
| Glu | Ala | His | Val | Gly | Ile | Asn | Gly | Glu | Ala | Asn | Leu | Asp | Phe | Leu | Asn | 385 | 390 | 395 | 400 |
| Ile | Pro | Leu | Thr | Ile | Pro | Glu | Met | Arg | Leu | Pro | Tyr | Thr | Ile | Ile | Thr | 405 | 410 | 415 | |
| Thr | Pro | Pro | Leu | Lys | Asp | Phe | Ser | Leu | Trp | Glu | Lys | Thr | Gly | Leu | Lys | 420 | 425 | 430 | |
| Glu | Phe | Leu | Lys | Thr | Thr | Lys | Gln | Ser | Phe | Asp | Leu | Ser | Val | Lys | Ala | 435 | 440 | 445 | |

SUBSTITUTE SHEET (RULE 26)

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| | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|
| Gln | Tyr | Lys | Lys | Asn | Lys | His | Arg | His | Ser | Ile | Thr | Asn | Pro | Leu | Ala | | |
| 450 | | | | | | 455 | | | | | 460 | | | | | | |
| Val | Leu | Cys | Glu | Phe | Ile | Ser | Gln | Ser | Ile | Lys | Ser | Phe | Asp | Arg | His | | |
| 465 | | | | | 470 | | | | | 475 | | | | | 480 | | |
| Phe | Glu | Lys | Asn | Arg | Asn | Asn | Ala | Leu | Asp | Phe | Val | Thr | Lys | Ser | Tyr | | |
| | | | | 485 | | | | | 490 | | | | | | 495 | | |
| Asn | Glu | Thr | Lys | Ile | Lys | Phe | Asp | Lys | Tyr | Lys | Ala | Glu | Lys | Ser | Gln | | |
| | | | 500 | | | | | 505 | | | | | 510 | | | | |
| Asp | Glu | Leu | Pro | Arg | Thr | Phe | Gln | Ile | Pro | Gly | Tyr | Thr | Val | Pro | Val | | |
| | | 515 | | | | | 520 | | | | | | 525 | | | | |
| Val | Asn | Val | Glu | Val | Ser | Pro | Phe | Thr | Ile | Glu | Met | Ser | Ala | Phe | Gly | | |
| | 530 | | | | | | 535 | | | | 540 | | | | | | |
| Tyr | Val | Phe | Pro | Lys | Ala | Val | Ser | Met | Pro | Ser | Phe | Ser | Ile | Leu | Gly | | |
| 545 | | | | | 550 | | | | | 555 | | | | | 560 | | |
| Ser | Asp | Val | Arg | Val | Pro | Ser | Tyr | Thr | Leu | Ile | Leu | Pro | Ser | Leu | Glu | | |
| | | | | 565 | | | | | 570 | | | | | | 575 | | |
| Leu | Pro | Val | Leu | His | Val | Pro | Arg | Asn | Leu | Lys | Leu | Ser | Leu | Pro | His | | |
| | | | 580 | | | | | 585 | | | | | | 590 | | | |
| Phe | Lys | Glu | Leu | Cys | Thr | Ile | Ser | His | Ile | Phe | Ile | Pro | Ala | Met | Gly | | |
| | | 595 | | | | | 600 | | | | | 605 | | | | | |
| Asn | Ile | Thr | Tyr | Asp | Phe | Ser | Phe | Lys | Ser | Ser | Val | Ile | Thr | Leu | Asn | | |
| | 610 | | | | | | 615 | | | | | 620 | | | | | |
| Thr | Asn | Ala | Glu | Leu | Phe | Asn | Gln | Ser | Asp | Ile | Val | Ala | His | Leu | Leu | | |
| 625 | | | | | 630 | | | | | 635 | | | | | 640 | | |
| Ser | Ser | Ser | Ser | Ser | Val | Ile | Asp | Ala | Leu | Gln | Tyr | Lys | Leu | Glu | Gly | | |
| | | | | 645 | | | | | 650 | | | | | | 655 | | |
| Thr | Thr | Arg | Leu | Thr | Arg | Lys | Arg | Gly | Leu | Lys | Leu | Ala | Thr | Ala | Leu | | |
| | | | 660 | | | | | 665 | | | | | | 670 | | | |
| Ser | Leu | Ser | Asn | Lys | Phe | Val | Glu | Gly | Ser | His | Asn | Ser | Thr | Val | Ser | | |
| | | 675 | | | | | 680 | | | | | 685 | | | | | |
| Leu | Thr | Thr | Lys | Asn | Met | Glu | Val | Ser | Val | Ala | Lys | Thr | Thr | Lys | Ala | | |
| | 690 | | | | | 695 | | | | | 700 | | | | | | |
| Glu | Ile | Pro | Ile | Leu | Arg | Met | Asn | Phe | Lys | Gln | Glu | Leu | Asn | Gly | Asn | | |
| 705 | | | | | 710 | | | | | 715 | | | | | 720 | | |
| Thr | Lys | Ser | Lys | Pro | Thr | Val | Ser | Ser | Ser | Met | Glu | Phe | Lys | Tyr | Asp | | |
| | | | | 725 | | | | | 730 | | | | | | 735 | | |

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Phe Asn Ser Ser Met Leu Tyr Ser Thr Ala Lys Gly Ala Val Asp His
 740 745 750
 Lys Leu Ser Leu Glu Ser Leu Thr Ser Tyr Phe Ser Ile Glu Ser Ser
 755 760 765
 Thr Lys Gly Asp Val Lys Gly Ser Val Leu Ser Arg Glu Tyr Ser Gly
 770 775 780
 Thr Ile Ala Ser Glu Ala Asn Thr Tyr Leu Asn Ser Lys Ser Thr Arg
 785 790 795 800
 Ser Ser Val Lys Leu Gln Gly Thr Ser Lys Ile Asp Asp Ile Trp Asn
 805 810 815
 Leu Glu Val Lys Glu Asn Phe Ala Gly Glu Ala Thr Leu Gln Arg Ile
 820 825 830
 Tyr Ser Leu Trp Glu His Ser Thr
 835 840

(2) INFORMATION FOR SEQ ID NO: 215:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 774 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 215:

Glu Phe Gln Leu Pro Arg Leu Ser His Thr Ile Glu Ile Pro Ala Phe
 1 5 10 15
 Gly Arg Leu His Gly Ile Leu Lys Ile Gln Ser Pro Leu Phe Ile Leu
 20 25 30
 Asp Ala Asn Ala Asn Ile Gln Asn Val Thr Thr Leu Glu Asn Lys Ala
 35 40 45
 Glu Ile Val Ala Ser Ile Ala Ala Thr Gly Glu Ser Glu Ile Glu Ala
 50 55 60
 Leu Asn Phe Asp Phe Gln Ala Gln Ala Gln Phe Leu Glu Leu Asn Pro
 65 70 75 80
 Asn Pro Leu Ile Leu Lys Glu Ser Met Asn Phe Ser Ser Lys His Ala
 85 90 95
 Arg Met Glu His Glu Gly Glu Ile Leu Phe Ser Gly Lys Phe Ile Glu
 100 105 110
 Gly Lys Leu Asp Thr Val Ala Ser Leu Gln Thr Glu Lys Asn Met Val
 115 120 125

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Phe | Asn | Asn | Gly | Met | Ile | Val | Lys | Ile | Asn | Asn | Pro | Ile | Ile | Leu | 130 | 135 | 140 | |
| Asp | Ser | His | Thr | Lys | Tyr | Phe | His | Lys | Leu | Ser | Ile | Pro | Arg | Leu | Asp | 145 | 150 | 155 | 160 |
| Phe | Ser | Ser | Lys | Ala | Ser | Phe | Asn | Asn | Glu | Ile | Lys | Met | Leu | Leu | Glu | 165 | 170 | 175 | |
| Ala | Gly | His | Val | Ala | Trp | Thr | Ser | Ser | Gly | Thr | Gly | Ser | Trp | Asn | Trp | 180 | 185 | 190 | |
| Ala | Cys | Pro | Asn | Phe | Ser | Asp | Glu | Gly | Thr | His | Ser | Ser | Lys | Ile | Ser | 195 | 200 | 205 | |
| Phe | Thr | Val | Glu | Gly | Pro | Ile | Ala | Phe | Phe | Gly | Leu | Ser | Asn | Asn | Ile | 210 | 215 | 220 | |
| Asn | Gly | Lys | His | Leu | Arg | Val | Ile | Gln | Lys | Leu | Ala | Tyr | Glu | Ser | Gly | 225 | 230 | 235 | 240 |
| Phe | Leu | Asn | Tyr | Ser | Met | Leu | Glu | Val | Glu | Ser | Lys | Val | Glu | Ser | Gln | 245 | 250 | 255 | |
| His | Val | Gly | Ser | Ser | Ile | Leu | Thr | Gly | Lys | Gly | Thr | Val | Leu | Leu | Arg | 260 | 265 | 270 | |
| Glu | Ala | Lys | Ala | Glu | Met | Thr | Gly | Glu | His | Asn | Ala | Asp | Leu | Asn | Gly | 275 | 280 | 285 | |
| Lys | Val | Ile | Gly | Thr | Leu | Lys | Asn | Ser | Leu | Ser | Phe | Ser | Ala | Gln | Pro | 290 | 295 | 300 | |
| Phe | Met | Ile | Thr | Ala | Ser | Thr | Asn | Asn | Asp | Gly | Asn | Leu | Lys | Val | Ser | 305 | 310 | 315 | 320 |
| Phe | Pro | Leu | Lys | Leu | Thr | Gly | Lys | Ile | Asp | Phe | Leu | Asn | Asn | Tyr | Ala | 325 | 330 | 335 | |
| Leu | Phe | Leu | Ser | Pro | His | Ala | Gln | Gln | Ala | Ser | Trp | Gln | Val | Ser | Ala | 340 | 345 | 350 | |
| Arg | Phe | Asn | Gln | Tyr | Lys | Tyr | Asn | Gln | Asn | Phe | Ser | Ala | Ile | Asn | Asn | 355 | 360 | 365 | |
| Glu | His | Asn | Ile | Glu | Ala | His | Val | Gly | Met | Asn | Gly | Asp | Ala | Asn | Leu | 370 | 375 | 380 | |
| Asp | Phe | Leu | Thr | Ile | Pro | Leu | Thr | Ile | Pro | Glu | Val | Lys | Leu | Pro | Tyr | 385 | 390 | 395 | 400 |
| Ile | Gly | Leu | Thr | Thr | Pro | Leu | Leu | Lys | Asp | Phe | Ser | Ile | Trp | Glu | Glu | 405 | 410 | 415 | |
| Thr | Gly | Leu | Lys | Lys | Gln | Ser | Phe | Asp | Leu | Ser | Val | Lys | Ala | Gln | Tyr | 420 | 425 | 430 | |

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Lys Lys Asn Arg Asp Arg His Ser Ile Ala Ile Pro Leu Asn Gly Phe
 435 440 445
 Tyr Glu Phe Ile Leu Asn Asn Val Asp Ser Gly Ile Gly Lys Ile Gly
 450 455 460
 Lys Val Arg Asp Ser Ala Leu Asp Tyr Leu Ile Ser Ser Tyr Asn Glu
 465 470 475 480
 Ala Lys Asn Lys Phe Glu Asn Ser Leu Ile Gln Pro Ser Arg Thr Phe
 485 490 495
 Gln Lys Arg Gly Tyr Thr Ile Pro Phe Val Asn Ile Glu Val Thr Pro
 500 505 510
 Phe Thr Val Glu Thr Leu Ala Ser Ser His Val Ile Pro Lys Ala Ile
 515 520 525
 Asn Thr Pro Ser Val His Ile Leu Gly Pro Asn Val Ile Val Pro Ser
 530 535 540
 Tyr Arg Leu Val Leu Pro Ser Leu Glu Leu Pro Val Leu Arg Val Pro
 545 550 555 560
 Arg Asn Leu Leu Lys Phe Ser Leu Pro Asp Phe Lys Glu Leu Arg Thr
 565 570 575
 Ile Asp Asn Ile Tyr Ile Pro Ala Leu Gly Asn Phe Thr Tyr Asp Phe
 580 585 590
 Ser Phe Lys Ser Ser Val Ile Thr Leu Asn Thr Asn Val Gly Leu Tyr
 595 600 605
 Asn Arg Ser Asp Ile Val Ala His Phe Leu Ser Ser Ser Ser Phe Val
 610 615 620
 Thr Asp Ala Leu Gln Tyr Lys Leu Glu Gly Thr Ser Arg Leu Thr Arg
 625 630 635 640
 Lys Arg Gly Leu Lys Leu Ala Thr Ala Asp Ser Leu Thr Asn Lys Phe
 645 650 655
 Val Lys Gly Asn His Asp Ser Thr Phe Ser Leu Thr Lys Lys Asn Met
 660 665 670
 Glu Ala Ser Val Lys Thr Thr Ala Asn Leu His Ala Pro Ile Leu Thr
 675 680 685
 Met Asn Phe Lys Gln Glu Leu Asn Gly Asn Ala Lys Ser Lys Pro Ile
 690 695 700
 Val Ser Ser Ser Ile Glu Leu Asn Tyr Asp Phe Asn Ser Ser Lys Leu
 705 710 715 720

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Tyr Ser Thr Ala Lys Gly Gly Val Asp His Lys Phe Ser Leu Glu Ser
 725 730 735
 Leu Thr Ser Tyr Phe Ser Ile Glu Ser Ser Thr Lys Gly Asn Ile Lys
 740 745 750
 Gly Ser Val Leu Ser Gln Glu Tyr Ser Gly Ser Val Ala Ser Glu Ala
 755 760 765
 Asn Thr Tyr Leu Asn Ser
 770

(2) INFORMATION FOR SEQ ID NO: 216:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 785 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 216:

Glu Phe Gln Leu Pro His Leu Ser His Thr Ile Glu Ile Pro Ala Phe
 1 5 10 15
 Gly Lys Leu His Ser Ile Leu Lys Ile Gln Ser Pro Leu Phe Ile Leu
 20 25 30
 Asp Ala Asn Ala Asn Ile Gln Asn Val Thr Thr Ser Gly Asn Lys Ala
 35 40 45
 Glu Ile Val Ala Ser Val Thr Ala Lys Gly Glu Ser Gln Phe Glu Ala
 50 55 60
 Leu Asn Phe Asp Phe Gln Ala Gln Ala Gln Phe Leu Glu Leu Asn Pro
 65 70 75 80
 His Pro Pro Val Leu Lys Glu Ser Met Asn Phe Ser Ser Lys His Val
 85 90 95
 Arg Met Glu His Glu Gly Glu Ile Val Phe Asp Gly Lys Ala Ile Glu
 100 105 110
 Gly Lys Ser Asp Thr Val Ala Ser Leu His Thr Glu Lys Asn Glu Val
 115 120 125
 Glu Phe Asn Asn Gly Met Thr Val Lys Val Asn Asn Gln Leu Thr Leu
 130 135 140
 Asp Ser His Thr Lys Tyr Phe His Lys Leu Ser Val Pro Arg Leu Asp
 145 150 155 160
 Phe Ser Ser Lys Ala Ser Leu Asn Asn Glu Ile Lys Thr Leu Leu Glu
 165 170 175

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| | | |
|---|-----|-----|
| Ala Gly His Val Ala Leu Thr Ser Ser Gly Thr Gly Ser Trp Asn Trp | | |
| 180 | 185 | 190 |
| Ala Cys Pro Asn Phe Ser Asp Glu Gly Ile His Ser Ser Gln Ile Ser | | |
| 195 | 200 | 205 |
| Phe Thr Val Asp Gly Pro Ile Ala Phe Val Gly Leu Ser Asn Asn Ile | | |
| 210 | 215 | 220 |
| Asn Gly Lys His Leu Arg Val Ile Gln Lys Leu Thr Tyr Glu Ser Gly | | |
| 225 | 230 | 235 |
| Phe Leu Asn Tyr Ser Lys Phe Glu Val Glu Ser Lys Val Glu Ser Gln | | |
| 245 | 250 | 255 |
| His Val Gly Ser Ser Ile Leu Thr Ala Asn Gly Arg Ala Leu Leu Lys | | |
| 260 | 265 | 270 |
| Asp Ala Lys Ala Glu Met Thr Gly Glu His Asn Ala Asn Leu Asn Gly | | |
| 275 | 280 | 285 |
| Lys Val Ile Gly Thr Leu Lys Asn Ser Leu Phe Phe Ser Ala Gln Pro | | |
| 290 | 295 | 300 |
| Phe Glu Ile Thr Ala Ser Thr Asn Asn Glu Gly Asn Leu Lys Val Gly | | |
| 305 | 310 | 315 |
| Phe Pro Leu Lys Leu Thr Gly Lys Ile Asp Phe Leu Asn Asn Tyr Ala | | |
| 325 | 330 | 335 |
| Leu Phe Leu Ser Pro Arg Ala Gln Gln Ala Ser Trp Gln Ala Ser Thr | | |
| 340 | 345 | 350 |
| Arg Phe Asn Gln Tyr Lys Tyr Asn Gln Asn Phe Ser Ala Ile Asn Asn | | |
| 355 | 360 | 365 |
| Glu His Asn Ile Glu Ala Ser Ile Gly Met Asn Gly Asp Ala Asn Leu | | |
| 370 | 375 | 380 |
| Asp Phe Leu Asn Ile Pro Leu Thr Ile Pro Glu Ile Asn Leu Pro Tyr | | |
| 385 | 390 | 395 |
| Thr Glu Phe Lys Thr Pro Leu Leu Lys Asp Phe Ser Ile Trp Glu Glu | | |
| 405 | 410 | 415 |
| Thr Gly Leu Lys Glu Phe Leu Lys Thr Thr Lys Gln Ser Phe Asp Leu | | |
| 420 | 425 | 430 |
| Ser Val Lys Ala Gln Tyr Lys Lys Asn Ser Asp Lys His Ser Ile Val | | |
| 435 | 440 | 445 |
| Val Pro Leu Gly Met Phe Tyr Glu Phe Ile Leu Asn Asn Val Asn Ser | | |
| 450 | 455 | 460 |
| Trp Asp Arg Lys Phe Glu Lys Val Arg Asn Asn Ala Leu His Phe Leu | | |
| 465 | 470 | 475 |
| | | 480 |

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Thr | Ser | Tyr | Asn | Glu | Ala | Lys | Ile | Lys | Val | Asp | Lys | Tyr | Lys | Thr | 485 | 490 | 495 | |
| Glu | Asn | Ser | Leu | Asn | Gln | Pro | Ser | Gly | Thr | Phe | Gln | Asn | His | Gly | Tyr | 500 | 505 | 510 | |
| Thr | Ile | Pro | Val | Val | Asn | Ile | Glu | Val | Ser | Pro | Phe | Ala | Val | Glu | Thr | 515 | 520 | 525 | |
| Leu | Ala | Ser | Arg | His | Val | Ile | Pro | Thr | Ala | Ile | Ser | Thr | Pro | Ser | Val | 530 | 535 | 540 | |
| Thr | Ile | Pro | Gly | Pro | Asn | Ile | Met | Val | Pro | Ser | Tyr | Lys | Leu | Val | Leu | 545 | 550 | 555 | 560 |
| Pro | Pro | Leu | Glu | Leu | Pro | Val | Phe | His | Gly | Pro | Gly | Asn | Leu | Phe | Lys | 565 | 570 | 575 | |
| Phe | Phe | Leu | Pro | Asp | Phe | Lys | Gly | Phe | Asn | Thr | Ile | Asp | Asn | Ile | Tyr | 580 | 585 | 590 | |
| Ile | Pro | Ala | Met | Gly | Asn | Phe | Thr | Tyr | Asp | Phe | Ser | Phe | Lys | Ser | Ser | 595 | 600 | 605 | |
| Val | Ile | Thr | Leu | Asn | Thr | Asn | Ala | Gly | Leu | Tyr | Asn | Gln | Ser | Asp | Ile | 610 | 615 | 620 | |
| Val | Ala | His | Phe | Leu | Ser | Ser | Ser | Ser | Phe | Val | Thr | Asp | Ala | Leu | Gln | 625 | 630 | 635 | 640 |
| Tyr | Lys | Leu | Glu | Gly | Thr | Ser | Arg | Leu | Met | Arg | Lys | Arg | Gly | Leu | Lys | 645 | 650 | 655 | |
| Leu | Ala | Thr | Ala | Val | Ser | Leu | Thr | Asn | Lys | Phe | Val | Lys | Gly | Ser | His | 660 | 665 | 670 | |
| Asp | Ser | Thr | Ile | Ser | Leu | Thr | Lys | Lys | Asn | Met | Glu | Ala | Ser | Val | Arg | 675 | 680 | 685 | |
| Thr | Thr | Ala | Asn | Leu | His | Ala | Pro | Ile | Phe | Ser | Met | Asn | Phe | Lys | Gln | 690 | 695 | 700 | |
| Glu | Leu | Asn | Gly | Asn | Thr | Lys | Ser | Lys | Pro | Thr | Val | Ser | Ser | Ser | Ile | 705 | 710 | 715 | 720 |
| Glu | Leu | Asn | Tyr | Asp | Phe | Asn | Ser | Ser | Lys | Leu | His | Ser | Thr | Ala | Thr | 725 | 730 | 735 | |
| Gly | Gly | Ile | Asp | His | Lys | Phe | Ser | Leu | Glu | Ser | Leu | Thr | Ser | Tyr | Phe | 740 | 745 | 750 | |
| Ser | Ile | Glu | Ser | Phe | Thr | Lys | Gly | Asn | Ile | Lys | Ser | Ser | Phe | Leu | Ser | 755 | 760 | 765 | |

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Gln Glu Tyr Ser Gly Ser Val Ala Asn Glu Ala Asn Val Tyr Leu Asn
 770 775 780

Ser
 785

(2) INFORMATION FOR SEQ ID NO: 217:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1056 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 217:

Glu Tyr Ser Gly Thr Ile Ala Ser Glu Ala Asn Thr Tyr Leu Asn Ser
 1 5 10 15

Lys Ser Thr Arg Ser Ser Val Lys Leu Gln Gly Thr Ser Lys Ile Asp
 20 25 30

Asp Ile Trp Asn Leu Glu Val Lys Glu Asn Phe Ala Gly Glu Ala Thr
 35 40 45

Leu Gln Arg Ile Tyr Ser Leu Trp Glu His Ser Thr Lys Asn His Leu
 50 55 60

Gln Leu Glu Gly Leu Phe Phe Thr Asn Gly Glu His Thr Ser Lys Ala
 65 70 75 80

Thr Leu Glu Leu Ser Pro Trp Gln Met Ser Ala Leu Val Gln Val His
 85 90 95

Ala Ser Gln Pro Ser Ser Phe His Asp Phe Pro Asp Leu Gly Gln Glu
 100 105 110

Val Ala Leu Asn Ala Asn Thr Lys Asn Gln Lys Ile Arg Trp Lys Asn
 115 120 125

Glu Val Arg Ile His Ser Gly Ser Phe Gln Ser Gln Val Glu Leu Ser
 130 135 140

Asn Asp Gln Glu Lys Ala His Leu Asp Ile Ala Gly Ser Leu Glu Gly
 145 150 155 160

His Leu Arg Phe Leu Lys Asn Ile Ile Leu Pro Val Tyr Asp Lys Ser
 165 170 175

Leu Trp Asp Phe Leu Lys Leu Asp Val Thr Thr Ser Ile Gly Arg Arg
 180 185 190

Gln His Leu Arg Val Ser Thr Ala Phe Val Tyr Thr Lys Asn Pro Asn
 195 200 205

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| | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---------|
| Gly | Tyr | Ser | Phe | Ser | Ile | Pro | Val | Lys | Val | Leu | Ala | Asp | Lys | Phe | Ile | 210 | 215 | 220 |
| Thr | Pro | Gly | Leu | Lys | Leu | Asn | Asp | Leu | Asn | Ser | Val | Leu | Val | Met | Pro | 225 | 230 | 235 240 |
| Thr | Phe | His | Val | Pro | Phe | Thr | Asp | Leu | Gln | Val | Pro | Ser | Cys | Lys | Leu | 245 | 250 | 255 |
| Asp | Phe | Arg | Glu | Ile | Gln | Ile | Tyr | Lys | Lys | Leu | Arg | Thr | Ser | Ser | Phe | 260 | 265 | 270 |
| Ala | Leu | Asn | Leu | Pro | Thr | Leu | Pro | Glu | Val | Lys | Phe | Pro | Glu | Val | Asp | 275 | 280 | 285 |
| Val | Leu | Thr | Lys | Tyr | Ser | Gln | Pro | Glu | Asp | Ser | Leu | Ile | Pro | Phe | Phe | 290 | 295 | 300 |
| Glu | Ile | Thr | Val | Pro | Glu | Ser | Gln | Leu | Thr | Val | Ser | Arg | Phe | Thr | Leu | 305 | 310 | 315 320 |
| Pro | Lys | Ser | Val | Ser | Asp | Gly | Ile | Ala | Ala | Leu | Asp | Leu | Asn | Ala | Val | 325 | 330 | 335 |
| Ala | Asn | Lys | Ile | Ala | Asp | Phe | Glu | Leu | Pro | Thr | Ile | Ile | Val | Pro | Glu | 340 | 345 | 350 |
| Gln | Thr | Ile | Glu | Ile | Pro | Ser | Ile | Lys | Phe | Ser | Val | Pro | Ala | Gly | Ile | 355 | 360 | 365 |
| Val | Ile | Pro | Ser | Phe | Gln | Ala | Leu | Thr | Ala | Arg | Phe | Glu | Val | Asp | Ser | 370 | 375 | 380 |
| Pro | Val | Tyr | Asn | Ala | Thr | Trp | Ser | Ala | Ser | Leu | Lys | Asn | Lys | Ala | Asp | 385 | 390 | 395 400 |
| Tyr | Val | Glu | Thr | Val | Leu | Asp | Ser | Thr | Cys | Ser | Ser | Thr | Val | Gln | Phe | 405 | 410 | 415 |
| Leu | Glu | Tyr | Glu | Leu | Asn | Val | Leu | Gly | Thr | His | Lys | Ile | Glu | Asp | Gly | 420 | 425 | 430 |
| Thr | Leu | Ala | Ser | Lys | Thr | Lys | Gly | Thr | Leu | Ala | His | Arg | Asp | Phe | Ser | 435 | 440 | 445 |
| Ala | Glu | Tyr | Glu | Glu | Asp | Gly | Lys | Phe | Glu | Gly | Leu | Gln | Glu | Trp | Glu | 450 | 455 | 460 |
| Gly | Lys | Ala | His | Leu | Asn | Ile | Lys | Ser | Pro | Ala | Phe | Thr | Asp | Leu | His | 465 | 470 | 475 480 |
| Leu | Arg | Tyr | Gln | Lys | Asp | Lys | Lys | Gly | Ile | Ser | Thr | Ser | Ala | Ala | Ser | 485 | 490 | 495 |
| Pro | Ala | Val | Gly | Thr | Val | Gly | Met | Asp | Met | Asp | Glu | Asp | Asp | Asp | Phe | 500 | 505 | 510 |

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| | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Lys | Trp | Asn | Phe | Tyr | Tyr | Ser | Pro | Gln | Ser | Ser | Pro | Asp | Lys | Lys | 515 | 520 | 525 |
| Leu | Thr | Ile | Phe | Lys | Thr | Glu | Leu | Arg | Val | Arg | Glu | Ser | Asp | Glu | Glu | 530 | 535 | 540 |
| Thr | Gln | Ile | Lys | Val | Asn | Trp | Glu | Glu | Glu | Ala | Ala | Ser | Gly | Leu | Leu | 545 | 550 | 555 |
| Thr | Ser | Leu | Lys | Asp | Asn | Val | Pro | Lys | Ala | Thr | Gly | Val | Leu | Tyr | Asp | 565 | 570 | 575 |
| Tyr | Val | Asn | Lys | Tyr | His | Trp | Glu | His | Thr | Gly | Leu | Thr | Leu | Arg | Glu | 580 | 585 | 590 |
| Val | Ser | Ser | Lys | Leu | Arg | Arg | Asn | Leu | Gln | Asn | Asn | Ala | Glu | Trp | Val | 595 | 600 | 605 |
| Tyr | Gln | Gly | Ala | Ile | Arg | Gln | Ile | Asp | Asp | Ile | Asp | Val | Arg | Phe | Gln | 610 | 615 | 620 |
| Lys | Ala | Ala | Ser | Gly | Thr | Thr | Gly | Thr | Tyr | Gln | Glu | Trp | Lys | Asp | Lys | 625 | 630 | 635 |
| Ala | Gln | Asn | Leu | Tyr | Gln | Glu | Leu | Leu | Thr | Gln | Glu | Gly | Gln | Ala | Ser | 645 | 650 | 655 |
| Phe | Gln | Gly | Leu | Lys | Asp | Asn | Val | Phe | Asp | Gly | Leu | Val | Arg | Val | Thr | 660 | 665 | 670 |
| Gln | Lys | Phe | His | Met | Lys | Val | Lys | His | Leu | Ile | Asp | Ser | Leu | Ile | Asp | 675 | 680 | 685 |
| Phe | Leu | Asn | Phe | Pro | Arg | Phe | Gln | Phe | Pro | Gly | Lys | Pro | Gly | Ile | Tyr | 690 | 695 | 700 |
| Thr | Arg | Glu | Glu | Leu | Cys | Thr | Met | Phe | Ile | Arg | Glu | Val | Gly | Thr | Val | 705 | 710 | 715 |
| Leu | Ser | Gln | Val | Tyr | Ser | Lys | Val | His | Asn | Gly | Ser | Glu | Ile | Leu | Phe | 725 | 730 | 735 |
| Ser | Tyr | Phe | Gln | Asp | Leu | Val | Ile | Thr | Leu | Pro | Phe | Glu | Leu | Arg | Lys | 740 | 745 | 750 |
| His | Lys | Leu | Ile | Asp | Val | Ile | Ser | Met | Tyr | Arg | Glu | Leu | Leu | Lys | Asp | 755 | 760 | 765 |
| Leu | Ser | Lys | Glu | Ala | Gln | Glu | Val | Phe | Lys | Ala | Ile | Gln | Ser | Leu | Lys | 770 | 775 | 780 |
| Thr | Thr | Glu | Val | Leu | Arg | Asn | Leu | Gln | Asp | Leu | Leu | Gln | Phe | Ile | Phe | 785 | 790 | 795 |

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|------|
| Gln | Leu | Ile | Glu | Asp | Asn | Ile | Lys | Gln | Leu | Lys | Glu | Met | Lys | Phe | Thr | 805 | 810 | 815 | |
| Tyr | Leu | Ile | Asn | Tyr | Ile | Gln | Asp | Glu | Ile | Asn | Thr | Ile | Phe | Asn | Asp | 820 | 825 | 830 | |
| Tyr | Ile | Pro | Tyr | Val | Phe | Lys | Leu | Leu | Lys | Glu | Asn | Leu | Cys | Leu | Asn | 835 | 840 | 845 | |
| Leu | His | Lys | Phe | Asn | Glu | Phe | Ile | Gln | Asn | Glu | Leu | Gln | Glu | Ala | Ser | 850 | 855 | 860 | |
| Gln | Glu | Leu | Gln | Gln | Ile | His | Gln | Tyr | Ile | Met | Ala | Leu | Arg | Glu | Glu | 865 | 870 | 875 | 880 |
| Tyr | Phe | Asp | Pro | Ser | Ile | Val | Gly | Trp | Thr | Val | Lys | Tyr | Tyr | Glu | Leu | 885 | 890 | 895 | |
| Glu | Glu | Lys | Ile | Val | Ser | Leu | Ile | Lys | Asn | Leu | Leu | Val | Ala | Leu | Lys | 900 | 905 | 910 | |
| Asp | Phe | His | Ser | Glu | Tyr | Ile | Val | Ser | Ala | Ser | Asn | Phe | Thr | Ser | Gln | 915 | 920 | 925 | |
| Leu | Ser | Ser | Gln | Val | Glu | Gln | Phe | Leu | His | Arg | Asn | Ile | Gln | Glu | Tyr | 930 | 935 | 940 | |
| Leu | Ser | Ile | Leu | Thr | Asp | Pro | Asp | Gly | Lys | Gly | Lys | Glu | Lys | Ile | Ala | 945 | 950 | 955 | 960 |
| Glu | Leu | Ser | Ala | Thr | Ala | Gln | Glu | Ile | Ile | Lys | Ser | Gln | Ala | Ile | Ala | 965 | 970 | 975 | |
| Thr | Lys | Lys | Ile | Ile | Ser | Asp | Tyr | His | Gln | Gln | Phe | Arg | Tyr | Lys | Leu | 980 | 985 | 990 | |
| Gln | Asp | Phe | Ser | Asp | Gln | Leu | Ser | Asp | Tyr | Tyr | Glu | Lys | Phe | Ile | Ala | 995 | 1000 | 1005 | |
| Glu | Ser | Lys | Arg | Leu | Ile | Asp | Leu | Ser | Ile | Gln | Asn | Tyr | His | Thr | Phe | 1010 | 1015 | 1020 | |
| Leu | Ile | Tyr | Ile | Thr | Glu | Leu | Leu | Lys | Lys | Leu | Gln | Ser | Thr | Thr | Val | 1025 | 1030 | 1035 | 1040 |
| Met | Asn | Pro | Tyr | Met | Lys | Leu | Ala | Pro | Gly | Glu | Leu | Thr | Ile | Ile | Leu | 1045 | 1050 | 1055 | |

(2) INFORMATION FOR SEQ ID NO: 218:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 989 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 218:

| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Ser | Lys | Gly | Thr | Arg | Ser | Ser | Val | Arg | Leu | Gln | Gly | Ala | Ser | Asn | 1 | 5 | 10 | 15 |
| Phe | Ala | Gly | Ile | Trp | Asn | Phe | Glu | Val | Gly | Glu | Asn | Phe | Ala | Gly | Glu | 20 | 25 | 30 | |
| Ala | Thr | Leu | Arg | Arg | Ile | Tyr | Gly | Thr | Trp | Glu | His | Asn | Met | Ile | Asn | 35 | 40 | 45 | |
| His | Leu | Gln | Val | Phe | Ser | Tyr | Phe | Asp | Thr | Lys | Gly | Lys | Gln | Thr | Cys | 50 | 55 | 60 | |
| Arg | Ala | Thr | Leu | Glu | Leu | Ser | Pro | Trp | Thr | Met | Ser | Thr | Leu | Leu | Gln | 65 | 70 | 75 | 80 |
| Val | His | Val | Ser | Gln | Pro | Ser | Pro | Leu | Phe | Asp | Leu | His | His | Phe | Asp | 85 | 90 | 95 | |
| Gln | Glu | Val | Ile | Leu | Lys | Ala | Ser | Thr | Lys | Asn | Gln | Lys | Val | Ser | Trp | 100 | 105 | 110 | |
| Lys | Ser | Glu | Val | Gln | Val | Glu | Ser | Gln | Val | Leu | Gln | His | Asn | Ala | His | 115 | 120 | 125 | |
| Phe | Ser | Asn | Asp | Gln | Glu | Glu | Val | Arg | Leu | Asp | Ile | Ala | Gly | Ser | Leu | 130 | 135 | 140 | |
| Glu | Gly | Gln | Leu | Trp | Asp | Leu | Glu | Asn | Phe | Phe | Leu | Pro | Ala | Phe | Gly | 145 | 150 | 155 | 160 |
| Lys | Ser | Leu | Arg | Glu | Leu | Leu | Gln | Ile | Asp | Gly | Lys | Arg | Gln | Tyr | Leu | 165 | 170 | 175 | |
| Gln | Ala | Ser | Thr | Ser | Leu | His | Tyr | Thr | Lys | Asn | Pro | Asn | Gly | Tyr | Leu | 180 | 185 | 190 | |
| Leu | Ser | Leu | Pro | Val | Gln | Glu | Leu | Thr | Asp | Arg | Phe | Ile | Ile | Pro | Gly | 195 | 200 | 205 | |
| Leu | Lys | Leu | Asn | Asp | Phe | Ser | Gly | Ile | Lys | Ile | Tyr | Lys | Lys | Leu | Ser | 210 | 215 | 220 | |
| Thr | Ser | Pro | Phe | Ala | Leu | Asn | Leu | Thr | Met | Leu | Pro | Lys | Val | Lys | Phe | 225 | 230 | 235 | 240 |
| Pro | Gly | Val | Asp | Leu | Leu | Thr | Gln | Tyr | Ser | Lys | Pro | Glu | Gly | Ser | Ser | 245 | 250 | 255 | |
| Val | Pro | Thr | Phe | Glu | Thr | Thr | Ile | Pro | Glu | Ile | Gln | Leu | Thr | Val | Ser | 260 | 265 | 270 | |
| Gln | Phe | Thr | Leu | Pro | Lys | Ser | Phe | Pro | Val | Gly | Asn | Thr | Val | Phe | Asp | 275 | 280 | 285 | |

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Asn | Lys | Leu | Thr | Asn | Leu | Ile | Ala | Asp | Val | Asp | Leu | Pro | Ser | Ile | 290 | 295 | 300 | |
| Thr | Leu | Pro | Glu | Gln | Thr | Ile | Glu | Ile | Pro | Ser | Leu | Glu | Phe | Ser | Val | 305 | 310 | 315 | 320 |
| Pro | Ala | Gly | Ile | Phe | Ile | Pro | Phe | Phe | Gly | Glu | Leu | Thr | Ala | His | Val | 325 | 330 | 335 | |
| Gly | Met | Ala | Ser | Pro | Leu | Tyr | Asn | Val | Thr | Trp | Ser | Thr | Gly | Trp | Lys | 340 | 345 | 350 | |
| Asn | Lys | Ala | Asp | His | Val | Glu | Thr | Phe | Leu | Asp | Ser | Thr | Cys | Ser | Ser | 355 | 360 | 365 | |
| Thr | Leu | Gln | Phe | Leu | Glu | Tyr | Ala | Leu | Lys | Val | Val | Gly | Thr | His | Arg | 370 | 375 | 380 | |
| Ile | Glu | Asn | Asp | Lys | Phe | Ile | Tyr | Lys | Ile | Lys | Gly | Thr | Leu | Gln | His | 385 | 390 | 395 | 400 |
| Cys | Asp | Phe | Asn | Val | Lys | Tyr | Asn | Glu | Asp | Gly | Ile | Phe | Glu | Gly | Leu | 405 | 410 | 415 | |
| Trp | Asp | Leu | Glu | Gly | Glu | Ala | His | Leu | Asp | Ile | Thr | Ser | Pro | Ala | Leu | 420 | 425 | 430 | |
| Thr | Asp | Phe | His | Leu | His | Tyr | Lys | Glu | Asp | Lys | Thr | Ser | Val | Ser | Ala | 435 | 440 | 445 | |
| Ser | Ala | Ala | Ser | Pro | Ala | Ile | Gly | Thr | Val | Ser | Leu | Asp | Ala | Ser | Thr | 450 | 455 | 460 | |
| Asp | Asp | Gln | Ser | Val | Arg | Leu | His | Val | Tyr | Phe | Arg | Pro | Gln | Ser | Pro | 465 | 470 | 475 | 480 |
| Pro | Asp | Asn | Lys | Leu | Ser | Ile | Phe | Lys | Met | Glu | Trp | Arg | Asp | Lys | Glu | 485 | 490 | 495 | |
| Ser | Asp | Gly | Glu | Thr | Tyr | Ile | Lys | Ile | Asn | Trp | Glu | Glu | Glu | Ala | Ala | 500 | 505 | 510 | |
| Phe | Arg | Leu | Leu | Asp | Ser | Leu | Lys | Ser | Asn | Val | Pro | Lys | Ala | Ser | Glu | 515 | 520 | 525 | |
| Ala | Val | Tyr | Asp | Tyr | Val | Lys | Lys | Tyr | His | Leu | Gly | His | Ala | Ser | Ser | 530 | 535 | 540 | |
| Glu | Leu | Arg | Lys | Ser | Leu | Gln | Asn | Asp | Ala | Glu | His | Ala | Ile | Arg | Met | 545 | 550 | 555 | 560 |
| Val | Asp | Glu | Met | Asn | Val | Asn | Ala | Gln | Arg | Val | Thr | Arg | Asp | Thr | Tyr | 565 | 570 | 575 | |

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| | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Ser | Leu | Tyr | Lys | Lys | Met | Leu | Ala | Gln | Glu | Ser | Gln | Ser | Ile | Pro | 580 | 585 | 590 |
| Glu | Lys | Leu | Lys | Lys | Met | Val | Leu | Gly | Ser | Leu | Val | Arg | Ile | Thr | Gln | 595 | 600 | 605 |
| Lys | Tyr | His | Met | Ala | Val | Thr | Trp | Leu | Met | Asp | Ser | Val | Ile | His | Phe | 610 | 615 | 620 |
| Leu | Lys | Phe | Asn | Arg | Val | Gln | Phe | Pro | Gly | Asn | Ala | Gly | Thr | Tyr | Thr | 625 | 630 | 635 |
| Val | Asp | Glu | Leu | Tyr | Thr | Ile | Ala | Met | Arg | Glu | Thr | Lys | Lys | Leu | Leu | 645 | 650 | 655 |
| Ser | Gln | Leu | Phe | Asn | Gly | Leu | Gly | His | Leu | Phe | Ser | Tyr | Val | Gln | Asp | 660 | 665 | 670 |
| Gln | Val | Glu | Lys | Ser | Arg | Val | Ile | Asn | Asp | Ile | Thr | Phe | Lys | Cys | Pro | 675 | 680 | 685 |
| Phe | Ser | Pro | Thr | Pro | Cys | Lys | Leu | Lys | Asp | Val | Leu | Leu | Ile | Phe | Arg | 690 | 695 | 700 |
| Glu | Asp | Leu | Asn | Ile | Leu | Ser | Asn | Leu | Gly | Gln | Gln | Asp | Ile | Asn | Phe | 705 | 710 | 715 |
| Thr | Thr | Ile | Leu | Ser | Asp | Phe | Gln | Ser | Phe | Leu | Glu | Arg | Leu | Leu | Asp | 725 | 730 | 735 |
| Ile | Ile | Glu | Glu | Lys | Ile | Glu | Cys | Leu | Lys | Asn | Asn | Glu | Ser | Thr | Cys | 740 | 745 | 750 |
| Val | Pro | Asp | His | Ile | Asn | Met | Phe | Phe | Lys | Thr | His | Ile | Pro | Phe | Ala | 755 | 760 | 765 |
| Phe | Lys | Ser | Leu | Arg | Glu | Asn | Ile | Tyr | Ser | Val | Phe | Ser | Glu | Phe | Asn | 770 | 775 | 780 |
| Asp | Phe | Val | Gln | Ser | Ile | Leu | Gln | Glu | Gly | Ser | Tyr | Lys | Leu | Gln | Gln | 785 | 790 | 795 |
| Val | His | Gln | Tyr | Met | Lys | Ala | Phe | Arg | Glu | Glu | Tyr | Phe | Asp | Pro | Ser | 805 | 810 | 815 |
| Val | Val | Gly | Trp | Thr | Val | Lys | Tyr | Tyr | Glu | Ile | Glu | Glu | Lys | Met | Val | 820 | 825 | 830 |
| Asp | Leu | Ile | Lys | Thr | Leu | Leu | Ala | Pro | Leu | Arg | Asp | Phe | Tyr | Ser | Glu | 835 | 840 | 845 |
| Tyr | Ser | Val | Thr | Ala | Ala | Asp | Phe | Ala | Ser | Lys | Met | Ser | Thr | Gln | Val | 850 | 855 | 860 |
| Glu | Gln | Phe | Val | Ser | Arg | Asp | Ile | Arg | Glu | Tyr | Leu | Ser | Met | Leu | Ala | 865 | 870 | 875 |

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Asp Ile Asn Gly Lys Gly Arg Glu Lys Val Ala Glu Leu Ser Ile Val
 885 890 895
 Val Lys Glu Arg Ile Lys Ser Trp Ser Thr Ala Val Ala Glu Ile Thr
 900 905 910
 Ser Asp Tyr Leu Arg Gln Leu His Ser Lys Leu Gln Asp Phe Ser Asp
 915 920 925
 Gln Leu Ser Gly Tyr Tyr Glu Lys Phe Val Ala Glu Ser Thr Arg Leu
 930 935 940
 Ile Asp Leu Ser Ile Gln Asn Tyr His Met Phe Leu Arg Tyr Ile Ala
 945 950 955 960
 Glu Leu Leu Lys Lys Leu Gln Val Ala Thr Ala Asn Asn Val Ser Pro
 965 970 975
 Tyr Leu Arg Phe Ala Gln Gly Glu Leu Ile Ile Thr Phe
 980 985

(2) INFORMATION FOR SEQ ID NO: 219:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 396 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 219:

Lys Asp Asn Val Phe Asp Gly Leu Val Arg Val Thr Gln Lys Phe His
 1 5 10 15
 Met Lys Val Lys His Leu Ile Asp Ser Leu Ile Asp Phe Leu Asn Phe
 20 25 30
 Pro Arg Phe Gln Phe Pro Gly Lys Pro Gly Ile Tyr Thr Arg Glu Glu
 35 40 45
 Leu Cys Thr Met Phe Ile Arg Glu Val Gly Thr Val Leu Ser Gln Val
 50 55 60
 Tyr Ser Lys Val His Asn Gly Ser Glu Ile Leu Phe Ser Tyr Phe Gln
 65 70 75 80
 Asp Leu Val Ile Thr Leu Pro Phe Glu Leu Arg Lys His Lys Leu Ile
 85 90 95
 Asp Val Ile Ser Met Tyr Arg Glu Leu Leu Lys Asp Leu Ser Lys Glu
 100 105 110
 Ala Gln Glu Val Phe Lys Ala Ile Gln Ser Leu Lys Thr Thr Glu Val
 115 120 125

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| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Arg | Asn | Leu | Gln | Asp | Leu | Leu | Gln | Phe | Ile | Phe | Gln | Leu | Ile | Glu | 130 | 135 | 140 | |
| Asp | Asn | Ile | Lys | Gln | Leu | Lys | Glu | Met | Lys | Phe | Thr | Tyr | Leu | Ile | Asn | 145 | 150 | 155 | 160 |
| Tyr | Ile | Gln | Asp | Glu | Ile | Asn | Thr | Ile | Phe | Asn | Asp | Tyr | Ile | Pro | Tyr | 165 | 170 | 175 | |
| Val | Phe | Lys | Leu | Leu | Lys | Glu | Asn | Leu | Cys | Leu | Asn | Leu | His | Lys | Phe | 180 | 185 | 190 | |
| Asn | Glu | Phe | Ile | Gln | Asn | Glu | Leu | Gln | Glu | Ala | Ser | Gln | Glu | Leu | Gln | 195 | 200 | 205 | |
| Gln | Ile | His | Gln | Tyr | Ile | Met | Ala | Leu | Arg | Glu | Glu | Tyr | Phe | Asp | Pro | 210 | 215 | 220 | |
| Ser | Ile | Val | Gly | Trp | Thr | Val | Lys | Tyr | Tyr | Glu | Leu | Glu | Glu | Lys | Ile | 225 | 230 | 235 | 240 |
| Val | Ser | Leu | Ile | Lys | Asn | Leu | Leu | Val | Ala | Leu | Lys | Asp | Phe | His | Ser | 245 | 250 | 255 | |
| Glu | Tyr | Ile | Val | Ser | Ala | Ser | Asn | Phe | Thr | Ser | Gln | Leu | Ser | Ser | Gln | 260 | 265 | 270 | |
| Val | Glu | Gln | Phe | Leu | His | Arg | Asn | Ile | Gln | Glu | Tyr | Leu | Ser | Ile | Leu | 275 | 280 | 285 | |
| Thr | Asp | Pro | Asp | Gly | Lys | Gly | Lys | Glu | Lys | Ile | Ala | Glu | Leu | Ser | Ala | 290 | 295 | 300 | |
| Thr | Ala | Gln | Glu | Ile | Ile | Lys | Ser | Gln | Ala | Ile | Ala | Thr | Lys | Lys | Ile | 305 | 310 | 315 | 320 |
| Ile | Ser | Asp | Tyr | His | Gln | Gln | Phe | Arg | Tyr | Lys | Leu | Gln | Asp | Phe | Ser | 325 | 330 | 335 | |
| Asp | Gln | Leu | Ser | Asp | Tyr | Tyr | Glu | Lys | Phe | Ile | Ala | Glu | Ser | Lys | Arg | 340 | 345 | 350 | |
| Leu | Ile | Asp | Leu | Ser | Ile | Gln | Asn | Tyr | His | Thr | Phe | Leu | Ile | Tyr | Ile | 355 | 360 | 365 | |
| Thr | Glu | Leu | Leu | Lys | Lys | Leu | Gln | Ser | Thr | Thr | Val | Met | Asn | Pro | Tyr | 370 | 375 | 380 | |
| Met | Lys | Leu | Ala | Pro | Gly | Glu | Leu | Thr | Ile | Ile | Leu | 385 | 390 | 395 | | | | | |

(2) INFORMATION FOR SEQ ID NO: 220:

(i) SEQUENCE CHARACTERISTICS:

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- (A) LENGTH: 433 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 220:

```

Ile Pro Gly Leu Ser Glu Lys Tyr Thr Gly Glu Glu Leu Tyr Leu Met
1           5           10           15

Thr Thr Glu Lys Ala Ala Lys Thr Ala Asp Ile Cys Leu Ser Lys Leu
          20           25           30

Gln Glu Tyr Phe Asp Ala Leu Ile Ala Ala Ile Ser Glu Leu Glu Val
          35           40           45

Arg Val Pro Ala Ser Glu Thr Ile Leu Arg Gly Arg Asn Val Leu Asp
          50           55           60

Gln Ile Lys Glu Met Leu Lys His Leu Gln Glu Lys Ile Arg Gln Thr
          65           70           75           80

Phe Val Thr Leu Gln Glu Ala Asp Phe Ala Gly Lys Leu Asn Arg Leu
          85           90           95

Lys Gln Val Val Gln Lys Thr Phe Gln Lys Ala Gly Asn Met Val Arg
          100          105          110

Ser Leu Gln Ser Lys Asn Phe Glu Asp Ile Lys Val Gln Met Gln Gln
          115          120          125

Leu Tyr Lys Asp Ala Met Ala Ser Asp Tyr Ala His Lys Leu Arg Ser
          130          135          140

Leu Ala Glu Asn Val Lys Lys Tyr Ile Ser Gln Ile Lys Asn Phe Ser
          145          150          155          160

Gln Lys Thr Leu Gln Lys Leu Ser Glu Asn Leu Gln Gln Leu Val Leu
          165          170          175

Tyr Ile Lys Ala Leu Arg Glu Glu Tyr Phe Asp Pro Thr Thr Leu Gly
          180          185          190

Trp Ser Val Lys Tyr Tyr Glu Val Glu Asp Lys Val Leu Gly Leu Leu
          195          200          205

Lys Asn Leu Met Asp Thr Leu Val Ile Trp Tyr Asn Glu Tyr Ala Lys
          210          215          220

Asp Leu Ser Asp Leu Val Thr Arg Leu Thr Asp Gln Val Arg Glu Leu
          225          230          235          240

Val Glu Asn Tyr Arg Gln Glu Tyr Tyr Asp Leu Ile Thr Asp Val Glu
          245          250          255

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Gly Lys Gly Arg Gln Lys Val Met Glu Leu Ser Ser Ala Ala Gln Glu
 260 265 270
 Lys Ile Arg Tyr Trp Ser Ala Val Ala Lys Arg Lys Ile Asn Glu His
 275 280 285
 Asn Arg Gln Val Lys Ala Lys Leu Gln Glu Ile Tyr Gly Gln Leu Ser
 290 295 300
 Asp Ser Gln Glu Lys Leu Ile Asn Val Ala Lys Met Leu Ile Asp Leu
 305 310 315 320
 Thr Val Glu Lys Tyr Ser Thr Phe Met Lys Tyr Ile Phe Glu Leu Leu
 325 330 335
 Arg Trp Phe Glu Gln Ala Thr Ala Asp Ser Ile Lys Pro Tyr Ile Ala
 340 345 350
 Val Arg Glu Gly Glu Leu Arg Ile Asp Val Pro Phe Asp Trp Glu Tyr
 355 360 365
 Ile Asn Gln Met Pro Gln Lys Ser Arg Glu Ala Leu Arg Asn Lys Val
 370 375 380
 Glu Leu Thr Arg Ala Leu Ile Gln Gln Gly Val Glu Gln Gly Thr Arg
 385 390 395 400
 Lys Trp Glu Glu Met Gln Ala Phe Ile Asp Glu Gln Leu Ala Thr Glu
 405 410 415
 Gln Leu Ser Phe Gln Gln Ile Val Glu Asn Ile Gln Lys Arg Met Lys
 420 425 430
 Thr

(2) INFORMATION FOR SEQ ID NO: 221:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 180 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 221:

Asp Met Thr Phe Ser Lys Gln Asn Ala Leu Leu Arg Ser Glu Tyr Gln
 1 5 10 15
 Ala Asp Tyr Glu Ser Leu Arg Phe Phe Ser Leu Leu Ser Gly Ser Leu
 20 25 30
 Asn Ser His Gly Leu Glu Leu Asn Ala Asp Ile Leu Gly Thr Asp Lys
 35 40 45

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Ile Asn Ser Gly Ala His Lys Ala Thr Leu Arg Ile Gly Gln Asp Gly
 50                               55                               60

Ile Ser Thr Ser Ala Thr Thr Asn Leu Lys Cys Ser Leu Leu Val Leu
65                               70                               75                               80

Glu Asn Glu Leu Asn Ala Glu Leu Gly Leu Ser Gly Ala Ser Met Lys
                               85                               90                               95

Leu Thr Thr Asn Gly Arg Phe Arg Glu His Asn Ala Lys Phe Ser Leu
                               100                              105                              110

Asp Gly Lys Ala Ala Leu Thr Glu Leu Ser Leu Gly Ser Ala Tyr Gln
                               115                              120                              125

Ala Met Ile Leu Gly Val Asp Ser Lys Asn Ile Phe Asn Phe Lys Val
                               130                              135                              140

Ser Gln Glu Gly Leu Lys Leu Ser Asn Asp Met Met Gly Ser Tyr Ala
145                               150                               155                               160

Glu Met Lys Phe Asp His Thr Asn Ser Leu Asn Ile Ala Gly Leu Ser
                               165                              170                              175

Leu Asp Phe Ser
                               180

```

(2) INFORMATION FOR SEQ ID NO: 222:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 142 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 222:

```

Asp Leu Thr Phe Ser Lys Gln Asn Ala Leu Leu Arg Ala Glu Tyr Gln
 1                               5                               10                               15

Ala Asp Tyr Lys Ser Leu Arg Phe Phe Thr Leu Leu Ser Gly Leu Leu
                               20                               25                               30

Asn Thr His Gly Leu Glu Leu Asn Ala Asp Ile Leu Gly Thr Asp Lys
                               35                               40                               45

Met Asn Thr Ala Ala His Lys Ala Thr Leu Arg Ile Gly Gln Asn Gly
                               50                               55                               60

Val Ser Thr Ser Ala Thr Thr Ser Leu Arg Tyr Ser Pro Leu Met Leu
65                               70                               75                               80

Glu Asn Glu Leu Asn Ala Glu Leu Ala Leu Ser Gly Ala Ser Met Lys
                               85                               90                               95

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Leu Ala Thr Asn Gly Arg Phe Lys Glu His Asn Ala Lys Phe Ser Leu
 100 105 110

Asp Gly Lys Ala Thr Leu Thr Glu Leu Ser Leu Gly Ser Ala Tyr Gln
 115 120 125

Ala Met Ile Leu Gly Ala Asp Ser Lys Asn Ile Phe Asn Phe
 130 135 140

(2) INFORMATION FOR SEQ ID NO: 223:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 420 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 223:

His Ile Phe Ile Pro Ala Met Gly Asn Ile Thr Tyr Asp Phe Ser Phe
 1 5 10 15

Lys Ser Ser Val Ile Thr Leu Asn Thr Asn Ala Glu Leu Phe Asn Gln
 20 25 30

Ser Asp Ile Val Ala His Leu Leu Ser Ser Ser Ser Ser Val Ile Asp
 35 40 45

Ala Leu Gln Tyr Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys Arg
 50 55 60

Gly Leu Lys Leu Ala Thr Ala Leu Ser Leu Ser Asn Lys Phe Val Glu
 65 70 75 80

Gly Ser His Asn Ser Thr Val Ser Leu Thr Thr Lys Asn Met Glu Val
 85 90 95

Ser Val Ala Lys Thr Thr Lys Ala Glu Ile Pro Ile Leu Arg Met Asn
 100 105 110

Phe Lys Gln Glu Leu Asn Gly Asn Thr Lys Ser Lys Pro Thr Val Ser
 115 120 125

Ser Ser Met Glu Phe Lys Tyr Asp Phe Asn Ser Ser Met Leu Tyr Ser
 130 135 140

Thr Ala Lys Gly Ala Val Asp His Lys Leu Ser Leu Glu Ser Leu Thr
 145 150 155 160

Ser Tyr Phe Ser Ile Glu Ser Ser Thr Lys Gly Asp Val Lys Gly Ser
 165 170 175

Val Leu Ser Arg Glu Tyr Ser Gly Thr Ile Ala Ser Glu Ala Asn Thr
 180 185 190

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Tyr Leu Asn Ser Lys Ser Thr Arg Ser Ser Val Lys Leu Gln Gly Thr
    195                                200                                205

Ser Lys Ile Asp Asp Ile Trp Asn Leu Glu Val Lys Glu Asn Phe Ala
    210                                215                                220

Gly Glu Ala Thr Leu Gln Arg Ile Tyr Ser Leu Trp Glu His Ser Thr
    225                                230                                235                                240

Lys Asn His Leu Gln Leu Glu Gly Leu Phe Phe Thr Asn Gly Glu His
    245                                250                                255

Thr Ser Lys Ala Thr Leu Glu Leu Ser Pro Trp Gln Met Ser Ala Leu
    260                                265                                270

Val Gln Val His Ala Ser Gln Pro Ser Ser Phe His Asp Phe Pro Asp
    275                                280                                285

Leu Gly Gln Glu Val Ala Leu Asn Ala Asn Thr Lys Asn Gln Lys Ile
    290                                295                                300

Arg Trp Lys Asn Glu Val Arg Ile His Ser Gly Ser Phe Gln Ser Gln
    305                                310                                315                                320

Val Glu Leu Ser Asn Asp Gln Glu Lys Ala His Leu Asp Ile Ala Gly
    325                                330                                335

Ser Leu Glu Gly His Leu Arg Phe Leu Lys Asn Ile Ile Leu Pro Val
    340                                345                                350

Tyr Asp Lys Ser Leu Trp Asp Phe Leu Lys Leu Asp Val Thr Thr Ser
    355                                360                                365

Ile Gly Arg Arg Gln His Leu Arg Val Ser Thr Ala Phe Val Tyr Thr
    370                                375                                380

Lys Asn Pro Asn Gly Tyr Ser Phe Ser Ile Pro Val Lys Val Leu Ala
    385                                390                                395                                400

Asp Lys Phe Ile Thr Pro Gly Leu Lys Leu Asn Asp Leu Asn Ser Val
    405                                410                                415

Leu Val Met Pro
    420

```

(2) INFORMATION FOR SEQ ID NO: 224:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 275 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 224:

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| | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|
| Met | Ala | Ser | Glu | Lys | Gly | Pro | Ser | Asn | Lys | Asp | Tyr | Thr | Leu | Arg | Arg | | |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | | | |
| Arg | Ile | Glu | Pro | Trp | Glu | Phe | Glu | Val | Phe | Phe | Asp | Pro | Gln | Glu | Leu | | |
| | | | 20 | | | | | 25 | | | | | 30 | | | | |
| Arg | Lys | Glu | Ala | Cys | Leu | Leu | Tyr | Glu | Ile | Lys | Trp | Gly | Ala | Ser | Ser | | |
| | | 35 | | | | | 40 | | | | | 45 | | | | | |
| Lys | Thr | Trp | Arg | Ser | Ser | Gly | Lys | Asn | Thr | Thr | Asn | His | Val | Glu | Val | | |
| | 50 | | | | | 55 | | | | | 60 | | | | | | |
| Asn | Phe | Leu | Glu | Lys | Leu | Thr | Arg | Lys | Glu | Ala | Cys | Leu | Leu | Tyr | Glu | | |
| 65 | | | | | 70 | | | | 75 | | | | | 80 | | | |
| Ile | Lys | Trp | Gly | Ala | Ser | Ser | Lys | Thr | Trp | Arg | Ser | Ser | Gly | Lys | Asn | | |
| | | | 85 | | | | | | 90 | | | | | 95 | | | |
| Thr | Thr | Asn | His | Val | Glu | Val | Asn | Phe | Leu | Glu | Lys | Leu | Thr | Ser | Glu | | |
| | | 100 | | | | | | 105 | | | | | 110 | | | | |
| Gly | Arg | Leu | Gly | Pro | Ser | Thr | Cys | Cys | Ser | Ile | Thr | Trp | Phe | Leu | Ser | | |
| | | 115 | | | | | 120 | | | | | 125 | | | | | |
| Trp | Ser | Pro | Cys | Trp | Glu | Cys | Ser | Met | Ala | Ile | Arg | Glu | Phe | Leu | Ser | | |
| | 130 | | | | | 135 | | | | | 140 | | | | | | |
| Gln | His | Pro | Gly | Val | Thr | Leu | Ile | Ile | Phe | Val | Ala | Arg | Leu | Phe | Gln | | |
| 145 | | | | | 150 | | | | 155 | | | | | 160 | | | |
| His | Met | Asp | Arg | Arg | Asn | Arg | Gln | Gly | Leu | Lys | Asp | Leu | Val | Thr | Ser | | |
| | | | 165 | | | | | 170 | | | | | | 175 | | | |
| Gly | Val | Thr | Val | Arg | Val | Met | Ser | Val | Ser | Glu | Tyr | Cys | Tyr | Cys | Trp | | |
| | | 180 | | | | | | 185 | | | | | 190 | | | | |
| Glu | Asn | Phe | Val | Asn | Tyr | Pro | Pro | Gly | Lys | Ala | Ala | Gln | Trp | Pro | Arg | | |
| | 195 | | | | | 200 | | | | | | 205 | | | | | |
| Tyr | Pro | Pro | Arg | Trp | Met | Leu | Met | Tyr | Ala | Leu | Glu | Leu | Tyr | Cys | Ile | | |
| | 210 | | | | 215 | | | | | | 220 | | | | | | |
| Ile | Leu | Gly | Leu | Pro | Pro | Cys | Leu | Lys | Ile | Ser | Arg | Arg | His | Gln | Lys | | |
| 225 | | | | 230 | | | | | 235 | | | | | 240 | | | |
| Gln | Leu | Thr | Phe | Phe | Ser | Leu | Thr | Pro | Gln | Tyr | Cys | His | Tyr | Lys | Met | | |
| | | | 245 | | | | | | 250 | | | | | 255 | | | |
| Ile | Pro | Pro | Tyr | Ile | Leu | Leu | Ala | Thr | Gly | Leu | Leu | Gln | Pro | Ser | Val | | |
| | | | 260 | | | | | 265 | | | | | 270 | | | | |
| Pro | Trp | Arg | | | | | | | | | | | | | | | |
| | | 275 | | | | | | | | | | | | | | | |

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(2) INFORMATION FOR SEQ ID NO: 225:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 589 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 225:

| | |
|---|-----|
| GGATCTGACG GTTCACTAAA CCAGCTCTGC TTATATAGAC CTCCCACCGT ACACGCCTAC | 60 |
| CGCCCATTGT CGTCAATGGG GCGGAGTTGT TACGACATTT TGGAAAGTCC CGTTGATTTT | 120 |
| GGTGCCAAAA CAAACTCCAT TGACGTCAAT GGGGTGGAGA CTTGGAAATC CCCGTGAGTC | 180 |
| AAACCGCTAT CCACGCCCCAT TGATGTACTG CCAAACCGC ATCACCATGG TAATAGCGAT | 240 |
| GACTAATACG TAGATGTACT GCCAAGTAGG AAAGTCCCAT AAGGTCATGT ACTGGGCATA | 300 |
| ATGCCAGGCG GGCCATTTAC CGTCATTGAC GTCAATAGGG GGCCTACTTG GCATATGATA | 360 |
| CACTTGATGT ACTGCCAAGT GGGCAGTTTA CCGTAAATAC TCCACCCATT GACGTCAATG | 420 |
| GAAAGTCCCT ATTGGCGTTA CTATGGGAAC ATACGTCATT ATTGACGTCA ATGGGCGGGG | 480 |
| GTCGTTGGGC GGTGAGCCAG GCGGGCCATT TACCGTAAGT TATGTAACGC GGAATCCAT | 540 |
| ATATGGGCTA TGAATAATG ACCCCGTAAT TGATTACTAT TAATAACTA | 589 |

(2) INFORMATION FOR SEQ ID NO: 226:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 35 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 226:

| | |
|--|----|
| GATCCAAATC ACCCACTGCA ACTCCTCCCC CTGCG | 35 |
|--|----|

(2) INFORMATION FOR SEQ ID NO: 227:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 227:

| | |
|------------------------------|----|
| GATCCATCCA ATTGGGCAAT CAGGAG | 26 |
|------------------------------|----|

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(2) INFORMATION FOR SEQ ID NO: 228:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 18 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 228:

GATCCGGTCT CCAATTGG

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(2) INFORMATION FOR SEQ ID NO: 229:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 34 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 229:

GATCCTCGGG AAAGGGAAAC CGAAACTGAA GCCG

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CLAIMS:

1. A composition comprising:
 - (a) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain; and
 - (b) a nucleic acid comprising an LDL or VLDL binding sequence, wherein said nucleic acid is bound to said polypeptide.
2. The composition of claim 1, wherein said polypeptide comprises an LDL nucleic acid binding domain.
3. The composition of claim 1, wherein said polypeptide comprises a VLDL nucleic acid binding domain.
4. The composition of claim 1, wherein said nucleic acid comprises an expression region operably linked to a promoter active in eukaryotic cells.
5. The composition of claim 4, wherein said expression region encodes a polypeptide.
6. The composition of claim 4, wherein said expression region comprises an antisense construct.
7. The composition of claim 5, wherein said polypeptide is selected from the group consisting of α -globin, β -globin, γ -globin, granulocyte macrophage-colony stimulating factor (GM-CSF), tumor necrosis factor (TNF), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, β -interferon, γ -interferon, cytosine deaminase, adenosine deaminase, β -glucuronidase, hypoxanthine guanine phosphoribosyl transferase, galactose-1-phosphate uridylyltransferase, glucocerebrosidase, glucose-6-phosphatase, thymidine kinase, lysosomal glucosidase, growth hormone, nerve growth factor, insulin, adrenocorticotrophic hormone, parathormone, follicle-stimulating hormone, luteinizing hormone, epidermal growth factor, thyroid stimulating

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hormone of CFTR, EGFR, VEGFR, IL-2 receptor, estrogen receptor, Bax, Bak, Bcl-X_s, Bik, Bid, Bad, Harakiri, Ad E1B, an ICE-CED3 protease neomycin resistance, luciferase, adenine phosphoribosyl transferase (APRT), retinoblastoma, insulin, mast cell growth factor, p53, p16, p21, MMAC1, p73, zac1 and BRCA1.

5

8. The composition of claim 6, wherein said antisense construct is complementary to a segment of an oncogene.

9. The composition of claim 8, wherein said oncogene is selected from the group consisting of *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl* and *abl*.

10

10. The composition of claim 4, wherein said promoter is selected from the group consisting of CMV IE, LTR, SV40 IE, HSV *tk*, β -actin, human globin α , human globin β and human globin γ promoter.

15

11. The composition of claim 1, wherein said nucleic acid binding domain is an apoB100 nucleic acid binding domain.

12. The composition of claim 1, wherein said composition further comprises one or more lipoproteins selected from the group consisting of apoA1, apoA-II, apoA-IV, acat, apoE, apoC-II, apoC-III and apo-D.

20

13. The composition of claim 11, wherein said apoB100 is selected from the group consisting of human, rat and baboon apoB100.

25

14. The composition of claim 1, wherein said polypeptide comprises at least two nucleic acid binding domains.

15. The composition of claim 14, wherein said nucleic acid binding domain contains a motif selected from the group consisting of a proline pipe helix DNA binding motif, a

30

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ISGF3 γ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motif and a nucleotide (ATP)-binding motif.

16. The composition of claim 14, wherein said binding domain is selected from the group consisting of SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, , SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166 and SEQ ID NO:175.
17. The composition of claim 1, wherein said polypeptide further comprises at least one nuclear localization sequence.
18. The composition of claim 17, wherein said nuclear localization sequence is from apoB100.
19. The composition of claim 17, wherein said nuclear localization sequence is selected from the group consisting of SEQ ID NO:178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210.
20. A method for expressing a polypeptide in a human cell comprising:

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- (a) providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) a nucleic acid comprising an expression cassette comprising a sequence encoding said polypeptide and a promoter active in eukaryotic cells, wherein said coding sequence is operably linked to said promoter, and wherein said nucleic acid sequence is bound to said LDL or VLDL;
- b) contacting said composition with said cell under conditions permitting transfer of said composition into said cell; and
- c) culturing said cell under conditions permitting the expression of said polypeptide.

21. The method of claim 20, wherein said polypeptide is a tumor suppressor.

22. The method of claim 20, wherein said polypeptide is a cytokine.

23. The method of claim 20, wherein said polypeptide is an enzyme.

24. The method of claim 20, wherein said polypeptide is a hormone.

25. The method of claim 20, wherein said polypeptide is a receptor.

26. The method of claim 20, wherein said polypeptide is an inducer of apoptosis.

27. The method of claim 21, wherein said tumor suppressor is selected from the group consisting of p53, p16, p21, MMAC1, p73, zac1, BRCA1 and Rb.

28. The method of claim 22, wherein said cytokine is selected from the group consisting of IL-2, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, TNF, GMCSF, β -interferon and γ -interferon.

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29. The method of claim 23, wherein said enzyme is selected from the group consisting of cytosine deaminase, adenosine deaminase, β -glucuronidase, hypoxanthine guanine phosphoribosyl transferase, galactose-1-phosphate uridylyltransferase, glucocerebrosidase, glucose-6-phosphatase, thymidine kinase and lysosomal glucosidase.
- 5
30. The method of claim 24, wherein said hormone is selected from the group consisting of growth hormone, nerve growth factor, insulin, adrenocorticotrophic hormone, parathormone, follicle-stimulating hormone, luteinizing hormone, epidermal growth factor and thyroid stimulating hormone.
- 10
31. The method of claim 25, wherein said receptor is selected from the group consisting of CFTR, EGFR, VEGFR, IL-2 receptor and the estrogen receptor.
32. The method of claim 26, wherein said inducer of apoptosis is selected from the group consisting of Bax, Bak, Bcl-X_s, Bik, Bid, Bad, Harakiri, Ad E1B and an ICE-CED3 protease.
- 15
33. The method of claim 20, wherein said promoter is selected from the group consisting of CMV IE, LTR, SV40 IE, HSV *tk*, β -actin, human globin α , human globin β and human globin γ promoter.
- 20
34. The method of claim 20, wherein said nucleic acid binding domain is an apoB100 nucleic acid binding domain.
35. The method of claim 20, wherein said apoB100 is selected from the group consisting of human, rat and baboon low density apoB100.
- 25
36. The method of claim 27, wherein said binding region is selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 γ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motifs, and a nucleotide (ATP)-binding motif.
- 30

37. The method of claim 20, wherein said polypeptide further comprises at least one nuclear localization sequence.
- 5 38. The method of claim 37, wherein said nuclear localization sequence is an apoB100 nuclear localization sequence.
39. The method of claim 20, wherein said polypeptide is selected from the group consisting of α -globin, β -globin, γ -globin, neomycin resistance, luciferase, adenine phosphoribosyl transferase (APRT), mast cell growth factor.
- 10 40. A method for providing an expression construct to a human cell comprising:
- (a) providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein said expression region is operably linked to said promoter, and wherein said nucleic acid sequence is bound to said LDL or VLDL;
- 15 (b) contacting said composition with said cell under conditions permitting transfer of said composition into said cell; and
- 20 (c) culturing said cell under conditions permitting the expression of said expression region.
41. The method of claim 40, wherein said expression construct comprises an antisense construct.
- 25 42. The method of claim 40, wherein said antisense construct is derived from an oncogene.
43. The method of claim 42, wherein said oncogene is selected from the group consisting *ras*, *myc*, *neu*, *raf*, *erb*, *src*, *fms*, *jun*, *trk*, *ret*, *gsp*, *hst*, *bcl* and *abl*.
- 30

44. The method of claim 40, wherein said expression construct comprises a nucleic acid coding for a gene.
45. The method of claim 44, wherein said gene encodes a polypeptide.
- 5 46. The method of claim 40, wherein said promoter is selected from the group consisting of CMV IE, LTR, SV40 IE, HSV *tk*, β -actin, human globin α , human globin β and human globin γ promoter.
- 10 47. The method of claim 40, wherein said nucleic acid binding domain is an apoB100 nucleic acid binding domain.
48. The method of claim 47, wherein said apoB100 is selected from the group consisting of human, rat and baboon low density apoB100.
- 15 49. The method of claim 48, wherein said DNA binding region is selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 γ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motifs, and a nucleotide (ATP)-binding motif.
- 20 50. The method of claim 40, wherein said polypeptide further comprises at least one nuclear localization sequence.
51. The method of claim 50, wherein said nuclear localization sequence is an apoB100
- 25 nuclear localization sequence.
52. The method of claim 40, wherein said gene encodes a polypeptide selected from the group consisting of α -globin, β -globin, γ -globin, green fluorescent protein, neomycin resistance, luciferase, adenine phosphoribosyl transferase (APRT), mast cell growth
- 30 factor.

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53. A method for treating a human disease comprising:
- a) providing a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein said expression region is operably linked to said promoter, and wherein said nucleic acid sequence is bound to said LDL or VLDL; and
 - b) administering said composition to a human subject having said disease under conditions permitting transfer of said composition into cells of said human subject.
54. The method of claim 53, wherein said disease is selected from the group consisting of cancer, diabetes, cystic fibrosis and arteriosclerosis.
55. The method of claim 53, wherein said promoter is selected from the group consisting of CMV IE, LTR, SV40 IE, HSV *tk*, β -actin, human globin α , human globin β and human globin γ promoter.
56. The method of claim 53, wherein said nucleic acid binding domain is an apoB100 binding domain.
57. The method of claim 56, wherein said apoB100 is selected from the group consisting of human, rat and baboon low density lipoprotein apoB100.
58. The method of claim 53, wherein said polypeptide comprises at least two nucleic acid binding regions.
59. The method of claim 58, wherein said binding region is selected from the group consisting of a proline pipe helix DNA binding motif, a ISGF3 γ -like DNA binding motif, a SREBP-like DNA binding motif, a coiled-coil motifs, and a nucleotide (ATP)-binding motif.

60. The method of claim 53, wherein said polypeptide comprises at least one nuclear localization sequence.
- 5 61. The method of claims 60, wherein said nuclear localization sequence is an apoB100 nuclear localization sequence.
62. The method of claim 53, wherein said nucleic acid encodes a gene.
- 10 63. The method of claim 53, wherein said expression construct comprises an antisense construct.
64. A pharmaceutical composition comprising:
- 15 (a) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain; and
- (b) a nucleic acid comprising an LDL or VLDL binding sequence, wherein said nucleic acid is bound to said polypeptide; said pharmaceutical composition being dispersed in a suitable diluent.
- 20 65. A method of transforming a cell comprising:
- a) providing a cell;
- b) contacting said cell with a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region
- 25 and a promoter active in eukaryotic cells, wherein said expression region is operably linked to said promoter, and wherein said nucleic acid sequence is bound to said LDL or VLDL;
- wherein expression of said expression region is indicative of said transformation.
- 30 66. A method of transfecting a cell comprising the steps of:
- a) providing a cell;

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b) contacting said cell with a composition comprising (i) an isolated polypeptide comprising at least one LDL or VLDL nucleic acid binding domain and (ii) an expression cassette comprising a nucleic acid sequence encoding an expression region and a promoter active in eukaryotic cells, wherein said expression region is operably
5 linked to said promoter, and wherein said nucleic acid sequence is bound to said LDL or VLDL; and
wherein expression of said expression region is indicative of said transfection.

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1: The Amino Acid Sequence of Apo B-100

| | | | | | | | | |
|-----------------|-----------|--------|--------|----------|---------|---------|---------|---------|
| 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 |
| EEEMLENVSLVCPKD | ATRFKHLRK | YTYN | YEAESS | SGVPGTAD | RSATRIN | CKVELEV | PQCSFIL | KTSQCTL |
| KEVYGFN | PEGKALLK | TKNSE | EEFAA | AMS | 100 | | | |
| RYELKLA | ITEGKQVFL | YPEKDE | PTYILN | IKRGIIS | ALLVPP | ETEEAKQ | VLFD | TVYGN |
| CSHTFV | TKRGN | VATEIS | TERDL | GQDRF | KPIRT | GISPL | AL | 200 |
| IKGMR | PLSTLI | SSSQ | CQYTL | DAKRKH | VAEAI | CKEQL | FLPF | SYN |
| KYGM | VAQV | TQTL | KL | EDTPK | INSR | FFGEG | TKMGL | AFES |
| TKST | SPKQ | AEAVL | K | 300 | | | | |
| TLQEL | KKLTISE | QNIQ | RANL | FNKL | VTELR | GLSDE | AVTSLL | PQ |
| IEV | SSPIT | LQAL | VQCG | QPQCS | THIL | QWL | KRVH | ANPL |
| IDV | VTYL | VAL | IPE | PSA | QQLR | 400 | | |
| EIF | NARD | QSR | ATL | YAL | SHAV | NNYH | KTNP | TGTQ |
| ELL | DI | ANYL | MEQ | IQDD | CTG | DED | TYL | ILRV |
| IGN | MG | Q | MEQL | TPEL | KSS | IL | KCV | QST |
| KPS | LM | IQ | KAA | 500 | | | | |
| IQAL | RKME | PKD | QEVLL | QTF | LDAS | PGDK | LAAYL | ML |
| MR | SP | QAD | INK | I | VQIL | PW | EQNE | QVKN |
| FV | ASH | TAN | IL | NS | EE | L | IQDL | KKL |
| VKE | AL | KES | QL | PTV | 600 | | | |
| MDFR | KFSR | NYQL | YKSV | SL | PD | ASAK | IEGNL | IFDP |
| NNYL | PK | ES | ML | KTTL | TA | GF | ASADL | IE |
| IG | LE | GK | GF | EPT | LEAL | FG | KQ | GF |
| PD | SV | NKAL | YW | NGQ | VP | 700 | | |
| DG | VSK | VL | VDH | GYT | KDD | KHEQ | DMV | NGIML |
| SVEKL | IKDL | KS | KEV | PEAR | AYLR | IL | GEEL | GFASL |
| HD | LQL | L | MG | ART | LQ | GI | PQ | MI |
| GEV | IR | KS | KN | DFL | 800 | | | |
| HYI | FME | NA | FEL | PT | GAG | LQ | LISS | SGV |
| IAP | GA | GV | KLE | VAN | MQAEL | VAK | PSV | SEF |
| V | TNM | GI | I | IPD | F | AR | SG | VQ |
| M | TN | FF | HES | G | LEA | H | VAL | KAG |
| KL | K | F | I | IP | 900 | | | |
| SPK | RP | KLL | SGG | N | TL | HL | VST | T |
| K | TE | V | IP | PL | IEN | RQ | SW | S |
| V | CK | Q | VP | GL | NY | CT | S | G |
| A | S | N | S | T | S | A | S | Y |
| P | L | TG | D | R | 1000 | | | |

| | | | | | | | | |
|----|----|----|------|----|------|------|------|------|
| 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 |
| AL | V | T | L | K | F | V | T | Q |
| A | E | G | A | K | Q | T | E | A |
| T | M | T | F | K | Y | N | R | Q |
| S | M | T | L | S | S | E | V | Q |
| I | P | D | F | V | D | L | G | T |
| I | L | R | V | N | D | E | S | T |
| E | G | K | T | S | Y | R | L | T |
| D | I | Q | N | K | K | I | T | E |
| V | A | L | M | G | H | L | S | C |
| D | T | K | E | E | R | K | I | G |
| V | I | S | I | P | 1100 | | | |
| R | L | Q | A | E | A | R | S | E |
| I | L | A | H | W | S | P | A | K |
| L | L | L | Q | M | D | S | A | T |
| A | Y | G | S | T | V | S | K | R |
| V | A | W | H | Y | D | E | E | K |
| I | E | F | E | W | I | N | T | G |
| T | N | V | D | T | K | M | T | S |
| N | F | P | V | D | L | S | D | Y |
| P | K | S | L | H | M | Y | A | N |
| R | L | D | H | R | V | P | E | T |
| D | M | T | F | R | H | V | G | 1200 |
| S | K | L | I | V | A | M | S | S |
| W | L | Q | K | A | G | S | L | P |
| Y | T | Q | T | L | Q | D | H | L |
| N | S | L | K | E | F | N | L | Q |
| N | M | G | L | P | D | F | H | I |
| P | E | N | L | F | L | K | S | D |
| G | R | V | K | Y | T | L | N | K |
| N | S | L | K | I | E | I | P | L |
| P | F | G | K | S | R | D | L | K |
| M | L | E | T | V | R | T | P | A |
| L | H | F | K | S | V | G | 1300 | |
| F | H | L | P | S | R | E | F | Q |
| V | P | T | F | T | I | P | K | L |
| Y | Q | L | Q | V | P | L | L | G |
| V | L | D | L | S | T | N | V | S |
| N | L | Y | N | W | S | A | S | Y |
| S | G | G | N | T | S | T | D | H |
| F | S | L | R | A | R | Y | H | M |
| A | D | S | V | D | L | S | Y | N |
| V | Q | G | S | G | E | T | T | Y |
| D | H | K | N | T | F | T | L | S |
| C | D | G | S | L | R | 1400 | | |
| H | K | F | L | D | S | N | I | K |
| F | S | H | V | E | K | L | G | N |
| N | P | V | S | K | G | L | L | I |
| F | D | A | S | S | W | G | P | Q |
| M | S | A | S | V | H | L | D | S |
| K | K | Q | H | L | F | V | K | E |
| V | K | I | D | G | Q | F | R | V |
| S | S | F | Y | A | K | G | T | Y |
| G | L | S | C | Q | R | P | N | T |
| G | R | L | N | G | E | S | N | L |
| R | F | N | S | S | Y | 1500 | | |
| Q | G | T | N | Q | I | T | G | R |
| E | D | G | T | L | S | L | T | S |
| D | L | Q | S | G | I | I | K | N |
| T | A | S | L | K | Y | E | N | Y |
| E | L | T | L | K | S | D | T | N |
| G | K | N | F | A | T | S | N | K |
| M | D | M | T | F | S | K | Q | N |
| A | L | L | R | S | E | Y | Q | A |
| D | E | S | L | R | F | F | S | L |
| S | G | S | L | N | S | H | G | L |
| E | L | N | 1600 | | | | | |
| A | D | I | L | G | T | D | K | I |
| N | S | G | A | H | K | A | T | L |
| R | I | G | Q | D | G | I | S | T |
| S | A | T | T | N | L | K | C | S |
| L | L | V | E | N | E | L | N | A |
| E | L | G | L | S | G | A | S | M |
| K | L | T | T | N | G | R | F | R |
| E | H | N | A | K | F | S | L | D |
| G | A | A | L | T | E | L | S | G |
| A | Y | A | M | I | L | G | V | D |
| S | K | N | I | F | 1700 | | | |
| N | F | K | V | S | Q | E | G | L |
| K | L | S | N | D | M | G | S | Y |
| A | E | M | K | F | D | H | T | N |
| S | L | N | I | A | G | L | S | L |
| D | N | I | Y | S | S | D | K | F |
| Y | Q | T | V | N | L | Q | P | Y |
| S | L | V | T | L | N | S | D | L |
| K | Y | N | A | L | D | L | T | N |
| N | G | K | L | R | E | P | L | K |
| L | H | V | A | G | N | L | 1800 | |
| K | G | A | Y | Q | N | N | E | I |
| K | H | I | Y | A | I | S | S | A |
| L | S | A | S | Y | K | A | D | T |
| V | A | K | V | Q | G | V | E | F |
| S | H | R | L | N | T | D | I | A |
| G | L | A | S | A | I | D | M | S |
| T | N | S | D | S | L | H | S | N |
| V | F | R | S | V | M | A | P | T |
| M | T | I | D | A | H | T | N | G |
| N | G | K | L | A | L | W | G | E |
| H | T | G | Q | L | 1900 | | | |
| Y | S | K | F | L | K | A | E | P |
| L | A | F | T | F | S | H | D | Y |
| K | G | S | T | S | H | L | V | S |
| R | K | S | I | S | A | A | L | E |
| H | K | V | S | A | L | L | T | P |
| A | E | Q | T | G | T | W | K | L |
| K | T | Q | F | N | N | E | Y | S |
| Q | D | L | D | A | Y | N | T | K |
| D | I | G | V | E | L | T | G | R |
| T | L | A | D | L | T | L | D | S |
| P | I | K | V | P | 2000 | | | |

FIG. 1A

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10 20 30 40 50 60 70 80 90
 LLLSEPINI IDALEMRDAVEKQPEFTTIVAFVKYKQNDVHSINL PFFETLQYEFERNRQTTI VVVENVQRNLKHINIDQFVRKYRAALGKL PQQANDYLN 2100
 SFNWERQVSHAKEKL TAL TKYRITENDIQIALDDAKINFNEKLSQLQTYMIQFDQYIKDSVDLHDLKIAIANI IDEIIEKLSLDEHYHIRVNLVKTIH 2200
 DLHLF IENIDFNKSGSSTASWIONVDTKYQIRIQIQEKLQQLKRHIQNIQIHLAGKLGKQHTIEAIDVRVLLDQLGTTISFERINDVLEHVKHVFINL IGD 2300
 FEVAEK INAFRAKVHEL IERYEVDQIQVLMOKLVEL THQYKLEKTIQKLSNVLQQVKTKDYFEKL VGFIDDAVKKLNELSKFTFIEDVNFKFLDML IKKL 2400
 KSFYHQFVDETNDKIREVTQRLNGEIQALELPQKAEALKLFLEETKATVAVYLESQDTKITL IINWLQEALSSASLAHMKAKFRETTLEDTRDRMYDMD 2500
 IQQELQRYLSLVGQVYSTLVYISDWWTLAANKL TDFAEQYSIQDWAKRMKALVEQGFVTPETIKTILGTMPAFEVSLQALQKATFQTPDFIVPL TDLRIP 2600
 SVQINFKDLKNIKIPSRFSTPEFTILNTFHIPSFTIDFVEMKVKIIRTIQDMQNSQLQWPPVDIYLRDLKVEDIPLARITLPDFRLPEIAIPEFIIPTLN 2700
 LNDQFVPLDHIPEFQLPHISHTIEVPTFGKLYSILKIQSPLETL DANADIGNGTTSANEAGIAASITAKGESKLEVLNDFQANAQLSNPKINPLALKES 2800
 VKFSSKYLRTHEHGSEMLFFGNAIEGKSNTVASLHTEKNTLELSNGVIVKINNQL TLDSENTKYFHKLNIPKLD FSSQADLRNEIKTLLKAGHIAWTSSGKG 2900
 SWKWACPRFSDEGTHESQISFTIEGPLTSFGLSNKINSKHLRVNQNL VYESGSLNFSKLEIQSQVDSQHVGHSVL TAKGMALFGEKGAEFTGRHDAHLNG 3000

10 20 30 40 50 60 70 80 90
 KVIIGTLKNSLFFSAQPFETASTNNEGNLKVRFPLRLTGKIDFLNNYALFLSPSAQASQVVSARFNQKYNQNF SAGNNENIMEAHVGINGEANLDFLN 3100
 IPLTIPEMRLPYTIIITTPPLKDFSLWEKTGLKEFLKTTKQSFDSL SVKAOYKKNKHRHSITNPLAVLCEFI SQSIKSFDRHFEKRNINNALDFVTKSYNETK 3200
 IKFDKYKAEKSHDELPRIFQIPGYTPVNVNVEVSPFTIEMSAFGVYFPAKAVSMPFSILGSDVRVPSYTL ILPSLELPVLHVPRNLKLSLPHFKELECTIS 3300
 HIFIPAMGNITYDFSFKSSVITLNTNAELFNQSDIVAHLL SSSSSVIDALQYKLEGTTRL TRKRGLKLATAISL SNKFVEGSHNSTVSLTTKNMEVSVAK 3400
 TTKAEIPILRMNFKQELNGNTKSKPTVSSSMEFKYDFNSSMLYSTAKGAVDHLKLSLESLTSYFSIESSTKGDVKGSVLSREYSGT IASEANTYLNKSTR 3500
 SSVKLQGTSKIDDIWNLEVKENFAGEATLQRIYSLWEHSTKNHLQLEGLFFTNGEHTSKATLELSPWQMSALVQVHASQPSSEHDFPDLGQEVALNANTK 3600
 NQKIRWKNEVR IHSGSFQSQVELSNDQEKALHDITAGSLEGHRLFLKNILPVYDKSLWDFLKL DVTTSGRRQHLRVSTAFVYTKNPNNGYSFIPVKVLA 3700
 DKFITPGLKNDLNSVLVMPFTFHVPTDLQVPSCKLDFREIQIYKKLRTSSFALNPLTPLEVKFPEVDVLTKYSQPEDSLIPFEITVPESQLTVSQFTL 3800
 PKSVSDGIAALDLNAVANKIADFELPTIIVPEQTIEIPSIKFSVPAGIVIPSFQAL TARFEVDSVPVYNATWSASLKNKADYVETVL DSTCSSTVQFLEVE 3900
 LNVLGTHKIEDGTLAGSKTGTLAHRDFAEYVEDGKFEGLEWEGKAHLN IKSFAFTDLHLRYQKDKKGISTSAASPAVGTGMDMDEDDDDFSKMNFFYS 4000

FIG. 1B

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| | | | | | | | | | |
|---|----------------|---------------------|---|---|------|----|----|----|--|
| 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | |
| PQSSPDKKLTIFKTEL RVRESDEETQIKVNWEEEAASGLL | TSLKDNVPKATGVL | YDYVNKYHWEHTGL | TLREVSSKLRRLQNNAEWYQGAIRQIDDD | 4100 | | | | | |
| VRFQKAASGTTGTGYQEWKDKAQNLYQELL | TQEGQASFOGL | KDNVFDGL | VRVTQKFHMKVKHL | IDSLIDFLNFPREFQPGKPGIYTR EELCTMFIREVGTV | 4200 | | | | |
| LSQVYSKVHNGSEILFSYFQDLVITL | PFELRKHKL | IDVISM YRELL | KDLSKEAQEVFKAIQSLKTTEVL | RNLQDLLQFIFQLIEDNIKQLKEMKFTYLIN | 4300 | | | | |
| YIQDEINTIFNDYIPYVFKLLKENL | CLNLHKFNEF | IQNELQEASQELQ | IIHQYIMALREEYFDPSIVGWT | VKYYELEEEKIVSLIKNLLVALKDFHSEYIV | 4400 | | | | |
| SASNFTSQLSSQVEQFLHRNIQEYLSIL | TPDGGGKEKIAEL | SATAQEIIKSQAIATKKII | ISDYHQQFRYKLLQDFSDQLSDYYEKFIAESKRLIDLSIQN | 4500 | | | | | |
| YHTFLIYITELLKKLQSTTVMPYMKLAPGEL | TIIL | | | | | | | | |

FIG. 1C

Comparison of SH3-like Regions in Apo B-100 to Known SH3 Domains of Signal Transduction Proteins. Percent similarities are indicated at Right margin.

| | | 10 | 20 | 30 | 40 | 50 | 60 | |
|------|--|----|----|----|----|----|----|----------------|
| B1 | KYTYNVEA--ESSGVPGTADSR-SATRINCKVELEVPQLCSFILKTSQ | | | | | | | (SEQ ID NO:3) |
| R9 | AYDFNPIKKDSSQLL-SVQQGETIYILN-KNSSGWDG--LVIDDSN | | | | | | | (SEQ ID NO:4) |
| | Y**NY * *SSS ** *** ** *N K *** S* | | | | | | | 55% |
| B2 | VYGFNPEGKALLKTKNSEEFAAAMSRVELKLAPEGKQV--FLYPE | | | | | | | (SEQ ID NO:5) |
| R33 | LYDFVASGDNTLSITKGEKLRVLGYNHYNGEWCEAQTNGQGWPVPSN | | | | | | | (SEQ ID NO:6) |
| | *Y F * G L TK ***** *y* * ** K* *** * | | | | | | | 51% |
| B3-1 | FLPFSYNNKYGMVAQVTQTLKLEDTPKINSRFF-GE-GTKKMGLAF | | | | | | | (SEQ ID NO:7) |
| R35 | LFDYKAQREDELT--FTKSAIIQNVEKQEGGWMRGDYGKKKQ-LWF | | | | | | | (SEQ ID NO:8) |
| | ** * ** * *T ** *** K * ** G* G KK L*F | | | | | | | 54% |
| B3-2 | FLPFSYNN-KYG-MVAQVTQTLKL-EDTPKINSRFF-GEGTKKM---GLA-FE | | | | | | | (SEQ ID NO:9) |
| R18 | LH--SYEPSHDGDLGFEKGEQLRILEQSGE-----WVKAQ-SLTTGQEGFIPFN | | | | | | | (SEQ ID NO:10) |
| | * SY* * G **** * L** E** ** ** * G** F* | | | | | | | 51% |

FIG. 2A

Comparison of SH3-like Regions in Apo B-100 to Known SH3 Domains of Signal Transduction Proteins. Percent similarities are indicated at Right margin.

| | | | |
|-----|--|----------------|-----|
| B4 | YTYLILRVIGNMGQTMEQLTPEL-KSSILKCVQSTKPSLMIQKAAIQALRKMEPKDKD---QEVLL | (SEQ ID NO:11) | |
| R52 | WVALFD-YAA-VNDR-DL--QVLKGE--K-LQVLRSTG--DWLARS�VTG--REGVYPSNFFVAP | (SEQ ID NO:12) | |
| | * *L* *** * * *L ** K K *Q * * ***** *L ** ** | | 50% |
| B5 | AFGFASADLIEIGLEGKGFEPTLEALFGKQGFPPDS-VN--KALYVWNGQVDP | (SEQ ID NO:13) | |
| R34 | LYDFAAENPDELTFNEGAVTVINKSNP-D-WW-EGELNGQRGVFPAS--YVE | (SEQ ID NO:14) | |
| | ***FA* ** E* ** ** ** * ** * *N ***** ** | | 59% |
| B8 | FGYTKDDKHEQ-DMVNGIMLSVEK--LIKDLKSK--EV-PEARAYLRILGEE | (SEQ ID NO:15) | |
| R25 | YDYKKEE--EDIDLHLGDILTVNKGSLVALGFGSDGQEAKEEIGWLNQY-NE | (SEQ ID NO:16) | |
| | * Y K** E* D* G ***V*K L** S E* PE **L * *E | | 56% |
| B8 | FDYHQFVDETNDK-IREVTQRLNGEIQ-ALELPQKAEALKFLEETKAT-V-AVYL | (SEQ ID NO:17) | |
| R32 | YDY-----QEKSPREVTMKK-GDILTLNLTNINK-DWVKVEVND-RQGFVPAAYV | (SEQ ID NO:18) | |
| | *DY **K *REV* * G*I *L* *K ***K* *** * V A*Y* | | 52% |

FIG. 2B

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| | | | |
|-------|---|----------------|-----|
| B9-1 | YDM--DIQQLQRYLSLVGQVYSTLVITYISDWT--LAAK-NLTDFAEQYSIQDWA | (SEQ ID NO:19) | |
| R35-2 | FDYKAQREDELTFTKSAIIQNVEKQDGG---WMRGDYGGKKQLW-FPSNY-VEEMI | (SEQ ID NO:20) | |
| | *** * **EL S** Q * W W ***K *L F* *Y ***** | | 54% |
| B9-2 | YMDIQ----QELQRYLSLVGQVYSTLVITYISDWTAAKNLTDFAEQ-YSIQDWAKRMK | (SEQ ID NO:21) | |
| R43 | IQ-DYEPRLTDEI-RI-SL-GEKVK-ILATHTDGLVEKCNTRKGTIHVSVD--KRYL | (SEQ ID NO:22) | |
| | *Q D** *E* R* SL G* * *** *D W L* K T * *S**D KR* | | 57% |
| B9-1 | YQMDI--QQELQ--RYLSLVGQVYSTLVITYIS-DWW---TLAA-KNLTDFAEQYSIQDWA | | |
| R49 | YDYEARTEDDLTFTK-----GEKF-HILNTEGDWEARSLSSGK--T--G-CIPSNYYVA | (SEQ ID NO:23) | |
| | Y**** *L * G* * ** D W *L** K T * * * *A | | 51% |
| B10 | TYDFSFK---SS-VITLNTNAE-LFNQSDIVAHLSSSSVIDALQY-----KLE | (SEQ ID NO:24) | |
| R9-2 | DFNYPICKDSSQLLSVQ-QGETIY----ILNK--NSS-GWWDGLVIDDSNGKVN | (SEQ ID NO:25) | |
| | DF ** K SS ***** **E ** I* * SS **D*L * K** | | 56% |
| B11 | KYDFNSSMLYSTAKGAVDHLKLSLESLTS-----YFSIESSTKGDVKGSVLSREY | (SEQ ID NO:26) | |
| R47 | EPYVAIK-AYTAVEGDEVSLLEGEAVEVIHKLIDGWWVIR---KDDVTGYFPSMYL | (SEQ ID NO:27) | |
| | * * *Y*** G L E** ** I K DV G **S * | | 50% |

FIG. 2C

Comparison of SH3-like Regions in Apo B-100 to Known SH3 Domains of Signal Transduction Proteins. Percent similarities are indicated at Right margin.

| | | | |
|------|---|----------------|-----|
| B12 | LWDFLKLD-----VTTSIGRRQHLRVSTA-----FVYTKNPNGYSFIPVKVLADKFITPGLKL | (SEQ ID NO:28) | |
| R3 | LYDF-KAEKADELTTYVG--ENL-FICAHNCEWFIK-PIGRGGPGL-VPVG-FVSI-IDI | (SEQ ID NO:29) | |
| | L*DF K** *TT *G * L * A ****K P G * * V** F*** * * | | 54% |
| B13 | LYDYVVKY-HWEHTGLT-LR-EVSSK-LRRNLQNNAEWVYQGAIRQIDDI | (SEQ ID NO:30) | |
| R3-2 | LYYDF--KAEKAD--LTTYVGENLFICAHN----CEWFI---AKPIGR | (SEQ ID NO:31) | |
| | LYYD* K* *** LT * E ***N EW** ** I * | | 51% |
| B14 | KPGIY--TREELCTMFIREVGTVL-----SQVYSKVHNGSE--ILF-SYFQ--DL | (SEQ ID NO:32) | |
| R36 | LFGFVPETKEELQ-VMPGNI VFVLKKGNDNIWATVM--F-NG-QKGLVPCNYLEPVEL | (SEQ ID NO:33) | |
| | **G* *T*EEL *** ** VL * V* * NG * *** *Y** *L | | 56% |
| B15 | GKPGIYTREELCTMFIREVGTVLSQ-----VYSKVHNGS-E---ILFS-YFQ--D | (SEQ ID NO:34) | |
| R59 | AKFDYVAQQEQE LDIKKNERLWLLDDSKSWW-RVRN-SMNKTGFVPSNYVERKN | (SEQ ID NO:35) | |
| | *K* *** *E * I* ** ** *Y*N S * ***S Y** * | | 53% |

FIG. 2D

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Identification of the regions of apo B-100 and the proteins compared in Figures 2A-2D.

| <u>Reference Protein Name:</u> | <u>SEQ ID NO.</u> |
|---|-------------------|
| Apo B-100 region B1 (aa 24-69) | SEQ ID NO:3 |
| r9 (aa 66-114). cell division control protein 25 gim 4857 | SEQ ID NO:4 |
| Apo B-100 region B2 (aa 75-119) | SEQ ID NO:5 |
| r33 (aa 69-114). Abl proto-oncogene tyrosine kinase (P150) gim 13887 | SEQ ID NO:6 |
| Apo B-100 region B3-1 (aa 240-283) | SEQ ID NO:7 |
| r35 (aa 799-841). 1-Phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma (PLC-gamma. PLC-II) gim 18895 | SEQ ID NO:8 |
| Apo B-100 region B3-2 (aa 240-284) | SEQ ID NO:9 |
| r18 (aa 69-114). Lck proto-oncogene tyrosine kinase (P56-LCK) gim 14213 | SEQ ID NO:10 |
| Apo B-100 region B4 (aa 457-518) | SEQ ID NO:11 |
| r52 (aa 57-109). BLK protein tyrosine kinase (B lymphocyte kinase) (P55-BLK) gim 13991. | SEQ ID NO:12 |
| Apo B-100 region B5 (aa 652-700) | SEQ ID NO:13 |
| r34 (aa 984-1031). Myosin IC heavy chain gim 16466 | SEQ ID NO:14 |
| Apo B-100 region B6 (aa 711-756) | SEQ ID NO:15 |
| r25 (aa 12-61). Phosphatidylinositol 3-OH gim 18072 | SEQ ID NO:16 |

FIG. 2E

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Identification of the regions of apo B-100 and the proteins compared in Figures 2A-2D.

| | |
|--|--------------|
| Apo B-100 region B9-1 (aa 2497-2547) | SEQ ID NO:19 |
| r35-2 (aa 800-850). 1-Phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma. (PLC-gamma. PLC-II) gim 18895 | SEQ ID NO:20 |
| Apo B-100 region B9-2 (aa 2497-2551) | SEQ ID NO:21 |
| r43 (aa 444-496). nuclear fusion protein FUS1 gim 9498 | SEQ ID NO:22 |
| r49 (aa 86-134). Fgr Proto-oncogene Tyrosine gim 14097 | SEQ ID NO:23 |
| Apo B-100 region B10 (aa 3311-3355) | SEQ ID NO:24 |
| r9-2 (aa 66-114). Cell division control protein 25 gim 4857 | SEQ ID NO:25 |
| Apo B-100 region B11 (aa 3434-3482) | SEQ ID NO:26 |
| r47 (aa 229-280). Neutrophil Cytosol Factor 1 (NCF-47K) gim 16659 | SEQ ID NO:27 |
| APO B-100 region B12 (aa 3657-3710) | SEQ ID NO:28 |
| r3 (aa 162-201)Bem-1 protein gim 3905 | SEQ ID NO:29 |
| Apo B-100 region B13 (aa 4053-4099) | SEQ ID NO:30 |
| r3-2 (aa 163-214)Bem-1 protein gim 3905 | SEQ ID NO:31 |
| Apo B-100 region B14 (aa 4180-4222) | SEQ ID NO:32 |
| r36 (aa 248-299). Neutrophil NADPH oxidase factor (P67-PHOX) gim 16660 | SEQ ID NO:33 |
| Apo B-100 region B15 (aa 4179-422) | SEQ ID NO:34 |
| r59. Cytoplasmic protein gim 16669 | SEQ ID NO:35 |

FIG. 2F

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Comparison of SH2-like Regions in Apo B-100 to Known SH2 Domains of Sign Transduction Proteins.

| | | | |
|-----|--|----------------|---|
| 9. | WYHASLTRAQAEHMLMRV-----PRDGA-FLVRKRNEPNSYAISFR-AEGKIKH | | |
| 10. | FFGEG-TK----KMGLAFESTKSTPPKQ-AEAVLKTLQELKKLTISEQNIQ-RANL | | |
| | ** T* *M * * P** A **** *E* ***S ** | | |
| 9. | C-RVQQEGTVMLGNSEFDSLVDLISYYEKHPL-----YRKMKLK | (SEQ ID NO:36) | |
| 10. | FNKLVTELRLGLSDEAVT-SLLPQLIEVSSPITLQALVQCGQPCSTHILQWLKRVHAN | (SEQ ID NO:37) | 4 |
| | ** E * ** SL* *LI * L ***** | | |
| 5. | WFHG--KISKQEAYNLLMTVGQACSFVRPS-DNTPGDY-SLYFRTSENIORFKICP | | |
| 11. | IMLSVEKLIKDLKSKE---VPEAR-AYLRILGEEL-G-FASLHDLQLLGKLLLMGAR | | |
| | ** K* K* V *A ***R* ** G * SL * | | |
| 5. | T----PNNQFMMGGRYYN-SSIGDIIDHYRK-EQIVEGY--LKEP | (SEQ ID NO:38) | |
| 11. | TLQGIPQ---MIGE-VIRKGSKNDFLLHYIFMENAFELPTGAGLQL | (SEQ ID NO:39) | 4 |
| | T P* M*G ** S D** HY E***E * ** | | |

FIG. 3A

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Comparison of SH2-like Regions in Apo B-100 to Known SH2 Domains of Sign Transduction Proteins.

5. WFHGKIS--KQEAYNLLMTVGQACSFLVRPSDNTPGDYSLYFRTSENIQ-----R--F
(SEQ ID NO:40)
16. YFH-KLNIPK---LD--FSS-QAD---LR--NEIK---TLL-KAGHIAWTSSGKGSW
FH K K K ** ** QA *R ** *L* ** * * * *
5. KI-CPTPNQFMGGRYNSSIGDIIDHYRKEQIVEGYLK
(SEQ ID NO:41)
16. KWACPRFSDE---GTH--ESQISFTIEGPLTSFGLSNKINS
K* CP * ** G * *S I I* * * *
6. WYWGDISR---EEVNE---KLRDTPDGTFLVRDASSKIQ--DYTLTLRKGGNNKL
(SEQ ID NO:42)
17. FFSAQPFEITASTNNEGNLKVR-----FPLR-LTGKIDFLNNYALFLSPSAQQAS
** *** NE K*R F**R ** KI* *Y*L L ***
6. IKVFHR--DGKYG--FSEPLTFCSVWDLITHRHESLAQYNAKLDTRLLYPVSKY
(SEQ ID NO:43)
17. WQVSARFNQYKYNQNFSAGNNEN-IMEA--HVGINGEANLDF-LNIPLTIPEMRL
* V R * KY FS **E* H* * A**** L** L *P **

FIG. 3B

Comparison of SH2-like Regions in Apo B-100 to Known SH2 Domains of Sign Transduction Proteins.

| | | |
|-----|--|----------------|
| 8. | WFHGKLGAG-RDGRHIAERLLTEYCIETGAPDGSFLVRESETFVGD-YTILSFWRNGK | |
| 21. | <u>FP-GKPGIYTRE</u> -----ELC----- <u>TMFIREVGTVLSQVYSK</u> --VHNGS | |
| | ** GK*G* R* E*C ****RE T** * Y* **NG | |
| 8. | VQHCR ¹ HSRQDAGTPKFFLTDNL-VFD--SLY-DLITH-----YQQVPLRCNEFEMRLSE | (SEQ ID NO:44) |
| 21. | -EILFSYF-QDLVITL ¹ PFELRKHKLIDVISMYRELL-KDLSKEAQEV-FKAIQS-LKTTE | (SEQ ID NO:45) |
| | * QD* *F **D S*Y *L* * Q*V ** * ** *E | |

Structurally important motifs are indicated by double underline. Percent similarity is :
right.

FIG. 3C

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Identification of the reference proteins as well as the apoB-100 regions used in the above alignments

| <u>Reference Protein Name:</u> | <u>Sequence ID No.</u> |
|--|------------------------|
| 9. = phospholipase C α 1. Residues 668-753 | SEQ ID NO:36 |
| 10. = Apo B-100 region 10. aa(271-377) | SEQ ID NO:37 |
| 5. = GTPASE-activating protein (GAP) (RAS P21 PROTEIN ACTIVATOR). Residues 348-437 | SEQ ID NO:38 |
| 11. = Apo B-100 region 11. aa(727-819) | SEQ ID NO:39 |
| 5. GTPASE-activating protein (GAP) (RAS P21 PROTEIN ACTIVATOR). Residues 348-435 | SEQ ID NO:40 |
| 16. = Apo B-100 region 16. aa(2861-2938) | SEQ ID NO:41 |
| 6. = p85 α . Residues 326-424 | SEQ ID NO:42 |
| 17. = Apo B-100 region 17. aa(3011-3110) | SEQ ID NO:43 |
| 8. = phospholipase C α 1. Residues 550-655 | SEQ ID NO:44 |
| 21. = Apo B-100 region 11. aa(4177-4267) | SEQ ID NO:45 |

FIG. 3D

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Comparison of the Apo B-100 SH1-like Region to SH1 Kinase Domains
Known Signal Transduction Proteins.

| | 10 | 20 | 30 | 40 | 50 | 60 | |
|------|------------|----------|------------|------------------|-------------|----------------|----------------------------------|
| V | G | * | ** | N* | VA | K | * |
| | | | | P | T* | VPE | *E* *K* *V * |
| APOB | VSDGIAALDL | ----- | NA | ----- | VANK | IADFELP | TIIVPEQTI-EIPSIK-FSVPAGIVIPSF |
| SRC | LGQCGFG | EVVMG | TWNG | T | TRVAIKTLK | ----- | PGTMS-PEAFLQEAQVMKKLRH-EKLV----- |
| cFYN | LGNGQFG | EVVMG | TWNG | NT | ---KVAIKTLK | ----- | PGTMS-PESFLEEAIIMKKLKH-DKLV----- |
| HCK | LGAGQFGE | VMMA | TYN | --- | KHTKVAVKTMK | ----- | PGMSV-EAFLAEANVMKTLQH-DKLVKLH- |
| LYN | LGAGQFG | EVVMGY | YN | NS | --TKVAVKTLK | ----- | PGTMSV-QAFLEEANIMKTLQH-DKLVRL-Y |
| LCK | LGAGQFG | EVVMGY | YNG | --- | HTKVAVKSLKQ | ----- | GSMS-PDAFLAEANIMKQLQH-QRLVRL-Y |
| | 70 | 80 | 90 | 100 | 110 | 120 | 130 |
| | *** | **** | * p*y *T * | * K | *** *L | ** * | ** ***** I *G |
| APOB | QAL | TARFEVDS | VPVYNAT | WSASLKNKADYVETVL | --- | DSTCSSTVQFL | ---EYELNVLGTHKIEDG |
| SRC | Q-LY-A | VVSEEP | IYIVTEY | MS-KG-S | LLD-FLK | GET-G-K | ---YLRLPQL-VDMAAQ--IASG |
| cFYN | Q-LY-A | VVSEEP | IYIVTEY | MN-KG-S | LLD-FLK | DGEG-RAL | ---KLPNL-VDMAAQ--VAAG |
| HCK | -AVVT-K | --- | E-PIYIITEF | MA-KG-S | LLD-FLK | SDE-GSKQP | -LPKL-----IDFSAQ--IAEG |
| LYN | -AVVT-R | --- | EEPIYIITEY | MA-KG-S | LLD-FLK | SDEGG-KVL-LPKL | -----IDFSAQ--IAEG |
| LCK | -AVVT | ----- | QEPIYIITEY | MEN-G-S | LVD-FLK | TPSGI-K-LTINKL | -----LDMAAQ--IAEG |

FIG. 4A

Identification of the Apo B-100 SH1-like Region and
the SH1 Kinase Domains of Known Signal Transduction
Proteins and Their Corresponding Sequence
Identification Numbers

| Reference Protein | Sequence ID No. |
|---------------------|-----------------|
| ApoB (aa 3804-4006) | SEQ ID NO:46 |
| SRC (aa 275-488) | SEQ ID NO:47 |
| FYN (275-488) | SEQ ID NO:48 |
| HCK (268-480) | SEQ ID NO:49 |
| LYN (252-469) | SEQ ID NO:50 |
| LCK (250-462) | SEQ ID NO:51 |

FIG. 4B

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The Inter-Krigle Proline-Rich Regions of Apo[a] are Compared to the Proline-Rich Region of SH3-Binding Protein 1 (3BP1).

| | | |
|-------|---|----------------|
| 3BP1 | TS-LRAPT-MPPP-LPPVPP-Q-PARRQSRR--LPA---SPVIS | (SEQ ID NO:57) |
| ikr2 | -SDAEG-TAVAPPTVTPVPSLEAPSE-QA-----PTEQR-PGVQE | (SEQ ID NO:58) |
| 3BP1 | TS-LRAPT-MPPP-LPPVPP-Q-PARRQSRR--LPA---SPVIS | (SEQ ID NO:57) |
| ikr3 | -SDAEG-TAVAPPTITPISLEAPSE-QA-----PTEQR-PGVQE | (SEQ ID NO:59) |
| 3BP1 | TS-LRAPT-MPPP-LPPVPP-Q-PARRQSRR--LPA---SPVIS | (SEQ ID NO:57) |
| ikr4 | -SDAEW-TAFVPPNVILAPSLEAFFE-QA-----L-TEE-TPGVQD | (SEQ ID NO:60) |
| 3BP1 | TS-LRAPT-MPPP-LPPVPP-Q-PARRQSRR--LPA---SPVIS | (SEQ ID NO:57) |
| ikr5 | ---L-V-TE--SSVLATLTVDPDPST-EASSEAPTEQ-SPGVQD | (SEQ ID NO:61) |
| 3BP1 | TS-LRAPT-MPPP-LPPVPP-Q-PARRQSRR--LPA---SPVIS | (SEQ ID NO:57) |
| ikr7 | P---VMESTLLTTPTVVPVPSTELPSE-EA-----PTEN-STGVQD | (SEQ ID NO:62) |
| 3BP1 | TS-LRAPT-MPPP-LPPVPP-Q-PARRQSRR--LPA---SPVIS | (SEQ ID NO:57) |
| ikr8 | P---VTESSVLTTPTVAPVPSTEAPSE-QA-----PP-E-KSPVVQD | (SEQ ID NO:63) |
| 3BP1 | TS-LRAPT-MPPP-LPPVPP-Q-PARRQSRR--LPA---SPVIS | (SEQ ID NO:57) |
| ikr9 | -SETE--SGVLET--PTVVP-E-PSM-EAHSEAPTEQ-TPVVRQ | (SEQ ID NO:64) |
| 3BP1 | TS-LRAPT-MPPP-LPPVPP-Q-PARRQSRR--LPA---SPVIS | (SEQ ID NO:57) |
| ikr10 | -SDTESGTVVAPPTV--I---QVPSL-----GPPSEQD- | (SEQ ID NO:65) |

FIG. 5A

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Identification of the Inter-Kringle Proline-Rich Regions
of Apo[a] and the Proline-Rich Region of SH3-Binding
Protein 1 (3BP1) compared in FIG. 5A.

| Reference Protein | Sequence ID No. |
|---|--------------------|
| 3BP1 | SEQ ID NO:57 |
| Proline-Rich Region of Sh3-Binding protein 1 | |
| ikr2 amino acids (106-141) | SEQ ID NO:58 |
| ikr3 amino acids (3322-3357) | SEQ ID NO:59 |
| ikr4 amino acids (3436-3471) | SEQ ID NO:60 |
| ikr5 amino acids (3550-3585) | SEQ ID NO:61 |
| ikr7 amino acids (3770-3805) | SEQ ID NO:62 |
| ikr8 amino acids (3884-3919) | SEQ ID NO:63 |
| ikr9 amino acids (3998-4033) | SEQ ID NO:64 |
| ikr10 amino acids (4112-4137) | SEQ ID NO:65 |

FIG. 5B

Proteins Are Compared to the Analogous Regions in Apo B-100.

| | | | | | | | | | | |
|----------------------|------------------|---------------|------|--------|-----------|----------|-----------|-----------|--------|----------------------|
| | *K*A*** | R* | **** | ** | **G* | G*** | * | * | *** | |
| B100(13-49) | PKDATRFKHLRKYTYN | YEAE | SSGV | -PGTAD | - | SRSATRI | (SEQ | ID | N0:66) | |
| SRC(7-40) | PKDAS | - | - | - | QRRRSLEP | -AENVHGA | -GGAF | PASQTPSKP | (SEQ | ID N0:67) |
| FYN(7-38) | DKEATKLTEERD | GSLN | - | - | - | Q | -SSGYRYGT | -DP | - | TPQHY (SEQ ID N0:68) |
| | *** | * | TF | Y* | *L | * | **T | *P | Y | PGE L |
| apoB-100 (4448-4536) | IQNYH-TFLIYITELL | KKLQ | STTV | MNP | -YMKLAPGE | -LTIIL | (SEQ | ID | N0:69) | |
| SRC(505-535) | PEE-RPTF | -EYLQAFLEDY | FTST | - | - | EPQYQ | - | - | PGENL | - |
| FYN(506-536) | PEE-RPTF | -EYLSQSFLEDY | FTAT | - | - | EPQYQ | - | - | PGENL | - |
| HCK(498-526) | PEE-RPTF | -EYIQSVLDDFY | TAT | - | - | ESQYQQQ | - | - | P | - |
| LYN(483-511) | AEE-RPTF | -DYLSQSVLDDFY | TAT | - | - | EGQYQQQ | - | - | P | - |
| LCK(480-508) | PED-RPTF | -DYLSRVLEDDFY | TAT | - | - | EGQYQPQ | - | - | P | - |

*indicates conserved amino acids

FIG. 6

Examples of Proline Pipe Helix Structures in ApoB-100

| SEQ ID NO: | Sequence | Sequence Source |
|------------|------------------------|----------------------------|
| 77 | PQNAKLKIKRPVKVQPIARVWY | Tus proline pipe (223-243) |
| 78 | PDFRLPEIAIPEFIIPTLNLD | ApoB-100 (2682-2702) |
| 79 | NDFQVPDLHIPEFQLPHISHTI | ApoB-100 (2702-2723) |
| 80 | PSLELPVLHVPRNLKLSLPHFK | ApoB-100 (3273-3294) |

FIG. 7

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Sequence Comparison of DNA-Binding Protein ISGF3 γ SEQ ID
 NO:81, and a Similar Region of Apo B-100 SEQ ID NO:82,
 Located Between Residues 0008 and 0393.

| | |
|---|----------------|
| MAS--GR <u>AR</u> CT-- <u>R</u> <u>K</u> <u>L</u> <u>R</u> <u>N</u> <u>W</u> <u>V</u> <u>E</u> <u>Q</u> <u>V</u> <u>E</u> <u>S</u> <u>G</u> --- <u>F</u> <u>P</u> <u>G</u> <u>V</u> <u>C</u> <u>W</u> <u>D</u> <u>D</u> <u>T</u> <u>A</u> - <u>K</u> <u>T</u> <u>M</u> <u>F</u> <u>R</u> <u>I</u> | ISGF3 γ |
| V <u>S</u> <u>L</u> <u>V</u> <u>C</u> <u>P</u> <u>K</u> <u>D</u> <u>A</u> - <u>T</u> <u>R</u> <u>F</u> <u>K</u> <u>H</u> <u>L</u> <u>R</u> <u>K</u> <u>Y</u> <u>T</u> <u>N</u> - <u>Y</u> <u>E</u> <u>A</u> <u>E</u> <u>S</u> <u>S</u> <u>G</u> <u>V</u> <u>P</u> <u>G</u> <u>T</u> <u>A</u> <u>D</u> <u>S</u> <u>R</u> <u>S</u> <u>A</u> <u>T</u> <u>R</u> <u>I</u> <u>N</u> <u>C</u> <u>K</u> <u>V</u> | apoB100 |
| ** * <u>T</u> ** <u>L</u> <u>R</u> * ** * <u>E</u> * * <u>P</u> <u>G</u> * <u>A</u> * ** | |
| PW-- <u>K</u> <u>H</u> <u>A</u> <u>G</u> <u>K</u> <u>Q</u> <u>D</u> <u>F</u> <u>R</u> <u>E</u> <u>S</u> <u>Q</u> <u>D</u> <u>A</u> <u>A</u> <u>F</u> <u>F</u> <u>K</u> <u>A</u> <u>W</u> <u>A</u> <u>I</u> <u>F</u> ---- <u>K</u> <u>G</u> <u>K</u> <u>Y</u> <u>K</u> --- <u>E</u> <u>G</u> <u>D</u> <u>K</u> <u>E</u> <u>V</u> <u>P</u> <u>E</u> <u>R</u> | ISGF3 γ |
| E <u>L</u> <u>E</u> <u>V</u> <u>P</u> <u>Q</u> <u>L</u> <u>C</u> <u>S</u> <u>F</u> <u>I</u> <u>L</u> <u>K</u> <u>T</u> <u>S</u> <u>Q</u> <u>T</u> <u>L</u> -- <u>K</u> <u>E</u> <u>V</u> <u>G</u> <u>F</u> <u>N</u> <u>P</u> <u>E</u> <u>G</u> <u>K</u> <u>A</u> <u>L</u> <u>L</u> <u>K</u> <u>K</u> <u>T</u> <u>K</u> <u>N</u> <u>S</u> <u>E</u> <u>E</u> <u>F</u> <u>A</u> <u>A</u> <u>A</u> | apoB100 |
| * * * ** <u>S</u> <u>Q</u> ** <u>K</u> ** <u>F</u> <u>K</u> * * <u>K</u> * * * ** | |
| G <u>R</u> <u>M</u> <u>D</u> <u>V</u> <u>A</u> <u>E</u> <u>P</u> <u>K</u> <u>V</u> <u>Y</u> <u>Q</u> <u>L</u> <u>L</u> <u>P</u> <u>P</u> <u>G</u> - <u>I</u> <u>V</u> <u>S</u> <u>G</u> <u>Q</u> <u>P</u> <u>G</u> <u>T</u> <u>Q</u> <u>K</u> <u>V</u> - <u>P</u> <u>S</u> ----- <u>K</u> <u>R</u> <u>Q</u> <u>H</u> <u>S</u> <u>S</u> <u>V</u> <u>S</u> <u>S</u> <u>E</u> | ISGF3 γ |
| <u>S</u> <u>R</u> <u>Y</u> <u>E</u> ---- <u>L</u> <u>K</u> <u>L</u> -- <u>A</u> <u>I</u> <u>P</u> <u>E</u> <u>G</u> <u>K</u> <u>Q</u> <u>V</u> <u>F</u> <u>L</u> <u>Y</u> <u>P</u> -- <u>E</u> <u>K</u> <u>D</u> <u>E</u> <u>P</u> <u>T</u> <u>Y</u> <u>I</u> <u>L</u> <u>N</u> <u>I</u> <u>K</u> <u>R</u> <u>G</u> <u>I</u> <u>I</u> <u>S</u> <u>A</u> <u>L</u> <u>L</u> <u>V</u> | apoB100 |
| <u>R</u> ** * <u>K</u> <u>V</u> ** <u>P</u> <u>G</u> <u>V</u> <u>P</u> * <u>K</u> * <u>P</u> * <u>K</u> <u>R</u> <u>S</u> * | |
| <u>R</u> <u>K</u> <u>E</u> - <u>E</u> <u>D</u> <u>A</u> <u>M</u> <u>Q</u> <u>N</u> <u>C</u> <u>T</u> <u>L</u> <u>S</u> <u>P</u> <u>S</u> <u>V</u> <u>L</u> <u>Q</u> <u>D</u> <u>S</u> <u>L</u> <u>N</u> <u>N</u> <u>E</u> <u>G</u> <u>A</u> <u>S</u> <u>G</u> <u>G</u> <u>A</u> <u>V</u> <u>H</u> <u>S</u> <u>D</u> <u>I</u> <u>G</u> <u>S</u> <u>S</u> <u>S</u> <u>S</u> <u>S</u> <u>S</u> <u>S</u> <u>P</u> <u>E</u> <u>P</u> | ISGF3 γ |
| <u>P</u> <u>P</u> <u>T</u> <u>E</u> <u>E</u> <u>A</u> <u>K</u> <u>Q</u> <u>V</u> <u>L</u> - <u>F</u> <u>L</u> <u>D</u> <u>T</u> <u>V</u> <u>Y</u> <u>G</u> <u>N</u> <u>C</u> <u>S</u> <u>T</u> <u>H</u> <u>T</u> <u>V</u> <u>K</u> <u>T</u> <u>R</u> <u>K</u> <u>G</u> <u>N</u> <u>V</u> <u>A</u> <u>T</u> <u>E</u> <u>I</u> <u>S</u> <u>T</u> <u>E</u> <u>R</u> <u>D</u> <u>L</u> <u>G</u> <u>Q</u> <u>C</u> <u>D</u> | apoB100 |
| <u>E</u> <u>E</u> * <u>A</u> <u>Q</u> * * <u>V</u> * * * * * * * * <u>S</u> * | |
| <u>Q</u> <u>E</u> <u>V</u> <u>T</u> <u>D</u> <u>T</u> <u>T</u> <u>E</u> <u>A</u> <u>P</u> <u>F</u> <u>Q</u> <u>G</u> <u>D</u> <u>Q</u> <u>R</u> <u>S</u> <u>L</u> <u>E</u> <u>F</u> <u>L</u> <u>L</u> <u>P</u> <u>P</u> <u>E</u> <u>P</u> <u>D</u> <u>Y</u> <u>S</u> <u>L</u> <u>L</u> <u>L</u> <u>T</u> <u>F</u> <u>I</u> <u>Y</u> <u>N</u> <u>G</u> <u>R</u> <u>V</u> <u>V</u> <u>G</u> <u>E</u> <u>A</u> <u>Q</u> <u>V</u> <u>Q</u> <u>S</u> | ISGF3 γ |
| <u>R</u> <u>F</u> <u>K</u> <u>P</u> <u>I</u> <u>R</u> <u>T</u> <u>G</u> <u>I</u> <u>S</u> <u>P</u> <u>A</u> <u>L</u> <u>I</u> <u>K</u> <u>G</u> <u>M</u> <u>T</u> <u>R</u> <u>P</u> <u>L</u> <u>S</u> <u>T</u> <u>L</u> <u>I</u> <u>S</u> <u>S</u> <u>Q</u> <u>S</u> <u>C</u> <u>Q</u> <u>Y</u> <u>T</u> <u>L</u> <u>D</u> <u>A</u> <u>K</u> <u>R</u> <u>K</u> <u>H</u> <u>V</u> <u>A</u> <u>E</u> <u>A</u> <u>I</u> <u>C</u> | apoB100 |
| <u>T</u> * * * * * * * * * <u>L</u> * * * * * * * * <u>A</u> ** | |

FIG. 8A

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Sequence Comparison of DNA-Binding Protein ISGF3 γ SEQ ID
 NO:81, and a Similar Region of Apo B-100 SEQ ID NO:82.
 Located Between Residues 0008 and 0393.

LDCRLVAEPGSESS-ME-QVLF-PKPGPEPTQRLLSQLERGILVASN ISGF3 γ
 KEQHFLFPFSYKNKYGMVAQVTQTLKL--EDTPKINSRFFGEGTKKMG apoB100
 -* K L** *S -* M QV *K* E T ** S -*

PRGLFVQ--RLCPIPISWNAPQAPPGPHLLPSNECVELFRTAYFCR ISGF3 γ
 --LAFESTKSTSPPKQAEAVLKTQLKLTISEQNIQ--RANLFNK apoB100
 L*** K *p- *A* - * K L *S** ** R* *F *

DLVRYFQGLGPPPKFQVTLNFWEESHGSSHTPQNLITVKMEQAFARYL ISGF3 γ
 -LVTELRLSDEAVTSLLPQLIEVSSPIT-LQALVQCGQPQCSTHTL apoB100
 LV *GL * * * ***E S * *Q L* Q ***L

KMEQAFARYLLEQ-TPEQQAAILSLV ISGF3 γ
 KRVHANP-LLIDVVTY---LVALIPE apoB100
K -A * L** T* ***L *

* indicates conserved amino acids
 bold type indicates positively charged, basic amino acids

FIG. 8B

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Sequence Comparison of DNA-Binding Protein ISGF3 γ SEQ ID NO:81, and a Similar Region of Apo B-100 Located Between Residues 2930 and 3324, SEQ ID NO:83.

| | |
|--|----------------|
| MA-SGRARCTKLRNWWVEQVESGQFPGVCWDD----- | ISGF3 γ |
| FGLSNKIN-SKHLRVNQLVYESGLNFSKLEIQSQVDSQHVGHSVL | apoB100 |
| ** S ** **LR *ESG * -** | |
| TAKTM-----FRIPW--KHAGKODFRESQDAAFFKAWAIFKGKYKEG | ISGF3 γ |
| TAKGMALFGEKAEFTGRHDAHLNGKVIIG-TL--KNSLFFSAQPF EI | apoB100 |
| TAK M ** * **H ** * ** R **F | |
| ---DKEVPE-RGRMDVAEPYKVYQLLPPGIVSGQPGTQKVPSKRQHS | ISGF3 γ |
| TASTNNEGNLKVRFPRLTGKI-DFLNNYALFLSPSAQQA-SWQVSA | apoB100 |
| * * * R* * - R* **L ** P *Q * S | |
| KRQHSSVSSE---RKEEDAMQNCTLSPSVLQDSLNNEEGASGGAVHS | ISGF3 γ |
| RFNQYKYNQNFSAQTNNENIMEAHVGINGEANLDFLNI-PLTIPEMR- | apoB100 |
| ** * -* * *E**M* - ** * N ** ** | |
| DIGSSSSSSPEPQEVTDTEAPFQGDORSLEFLLPPEPDYSLLLTF | ISGF3 γ |
| -LPYTIITTPPLKDFSLWEKTGLKEFL-KTTKQSFDSL VKAQYKKNK | apoB100 |
| * * * ** P -* \ / - **-* ** * * * -* | |

FIG. 8C

ISGF3 γ
apoB100

* indicates conserved amino acids
bold type indicates positively charged, basic amino acids
ISGF3γ = sequence ID No:81. Apo B-100 amino acids (aa
2930-3324) = sequence ID N0:83.

FIG. 8D

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Various regions of apoB-100 having similarity of ISGF3 γ (1-51)

| SEQ ID NO: | | |
|------------|-----------------------|---|
| 84 | ISGF3 γ (1-51) | MASGRARCTRKLRN $\overline{\text{VVEQVESGQFPGVCWDDTAKTMRIPWKHAGKQDFR}}$ |
| 85 | APOB(13-59) | --PKDATRFKHLRK $\overline{\text{YTYNVEAESGSGVPGTAD-SRSATRINCKVELEVLPQ}}$ |
| 86 | APOB(80-116) | --PEGKALLK $\overline{\text{TKNSEEFAAAM}}\text{-----SR\overline{\text{YELKLAIP-EGKQVFL}}-----}$ |
| 87 | APOB(159-196) | --CSTHFTVK $\overline{\text{TRKGNVATEIST}}\text{-----ERDLGQCDFKPIRTGIS}$ |
| 88 | APOB(363-413) | CSTHILQWLK $\overline{\text{RVHANPLLIDWVTYVALIPEPSAQQRLREIFNMARDQRSRA}}$ |
| 89 | APOB(1082-1119) | HLSCDTKEERK $\overline{\text{IKGVISI}}\text{-----PRLQAEARSEILAHWSPAKL}$ |
| 90 | APOB(1441-1487) | --SVHLDSKKKQHL $\overline{\text{FVKEVKIDGQFRVSSFY--AKGTYGLSCQRPNTGRL}}$ |
| 91 | APOB(2073-2113) | KHINIDQFVRKY $\overline{\text{RAALGKLPPQANDYLSFNWERQVSHAKE}}\text{-----}$ |
| 92 | APOB(2114-2153) | ---KL $\overline{\text{TALTKKYRITENDIQIA}}\text{-----LDDAKINFNEKLSQLQTYMIQ}$ |
| 93 | APOB(2281-2330) | -ERINDVLEHV $\overline{\text{KHFVINLIGDFEVAEKINAFRAKVHELIERYEVDQIQVL}}$ |
| 94 | APOB(2390-2439) | -NKFLDMLIK $\overline{\text{KLKSFYHQFVDETNDKIREVTQRLNGEIQALELPQKAEAL}}$ |
| 95 | APOB(2933-2955) | ---SNK $\overline{\text{INSKHLRVNQNLVYESGSLN}}\text{-----}$ |
| 96 | APOB(2956-3001) | ----FSKLEIQSQVDSQ $\overline{\text{HVGHSVLTAKGMALFEGGKAEFTGRHDAHLNGK}}$ |

FIG. 9A

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Various regions of apoB-100 having similarity of ISGF3 γ (1-51)

| | |
|---|-----|
| KLDVTTSIGRRQHLRVSTAFVYTKNPNGYSFSIPVKVLADKFITPGLKLND | 99 |
| --FREIQIYKKLRTSSFALNPTLPEVKFPEVDVLTKYSQPEDSLIPFFEI | 100 |
| ---LHLRYQKDKKGGISTSAASPAVGTVGMDMDEDDDFSKWNFYSPQSSPD | 101 |
| ---LREVSSKLRRNLQNNAEWVYQGAIRQIDDIDVRFQKAASGTTGTQEW | 102 |
| -RVTQKFHMKVKHLIDSLIDFLNFPFQPGKPGIYTREELCTMFIREVGT | 103 |

FIG. 9B

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Various regions of apoB-100 having similarity of ISGF3 γ (42-69)

| | SEQ ID NO: |
|--|----------------------------|
| WKHAGKQDFRESQDAFF-----KAWAIFKGK $\overline{\text{Y}}$ KEG-DKEVPERGRMDVAEPYK $\overline{\text{K}}$ | iSGF3 γ (42-69) 104 |
| EHVKHFVINLIGD-----FEVAEKINA-FRAKVHELIERYEVDQIQVLM $\overline{\text{D}}$ KL $\overline{\text{V}}$ | APOB(2288-2335) 105 |
| VRKYRAALGKLPQQANDYLSFNWERQVS--HAKEKLTALTKKYRITENDIQIA | APOB(2081-2132) 106 |
| YTKDSYDLHDLKIAIANIIDEITEKLSLDEHYHIRVNLVKTIHDLHLFIENIDFNK $\overline{\text{K}}$ | APOB(2157-2213) 107 |
| -----KITLIIINWLQEALSSASLAHMKAKFRETLEDTR----- | APOB(2461-2493) 108 |
| -----TDHFSLRARYHMKADSVVDLSYNVQSGSETTY | APOB(1353-1385) 109 |
| -----KLTNGRFREHNAKFSLDGK----- | APOB(1656-1675) 110 |
| DTKYQIRIQIQEK $\overline{\text{L}}$ QQLKRHIQNIDIQHLAGKLKQHIEAIDVRVLLDQLGTT----- | APOB(2226-2277) 111 |
| -----FHDFPDLGQEQVALNANTKNQKIRWKNEVR $\overline{\text{I}}$ HSGSFQSQVELSNDQ $\overline{\text{K}}$ | APOB(3583-3627) 112 |
| -----KDNVFDGLVRVTQKF $\overline{\text{H}}$ MKV $\overline{\text{K}}$ HLIDSLIDFLNFP $\overline{\text{R}}$ ----- | APOB(4141-4174) 113 |
| -----HRNIQEYLSILTPDPGKGK $\overline{\text{E}}$ KIAELSAQAQEI $\overline{\text{I}}$ KS----- | APOB(4418-4452) 114 |

FIG. 9C

Sequence Comparison of DNA-Binding Domains of SREBP 1 (aa 279-452) SEQ ID NO:116, SREBP 2 (aa 287-568) SEQ ID NO:117 and ADD1 (aa 250-421) SEQ ID NO:118 to a Similar Region of Apo B-100 (aa 2024-2234) SEQ ID NO:115.

| | |
|---|---------|
| EFTIVAFVKYDKNQDVHSINLPFFETLQEFYFERNRQTIIIVLENVQ | APOB100 |
| GPLPTLVSGGTILATVPLVVDAEKLPINRLAAGSKAPASAQSR-GE | SREBP1 |
| QVPTLVGSSGTILTTMPVMGQEKVP IKQVPGGVKQ -LEPPKE-GE | SREBP2 |
| GPLQTLVSGGTILATVPLVVDTKLP I HLAAGGKALGSAQSR-GE | ADD1 |
| ***** V * * * ***** *Q * ** E * | |
| RKLKHINIDQFVRKYRAAL-GKLPQQANDYLN S FNW ERQV SHAKEK | APOB100 |
| KRTAH-NAIE--KRYRSSINDK I IELK-DLVGTEAKLNKSAVLRK | SREBP1 |
| RRTH-N I IE--KRYRSSINDK I IELK-DLVMGTD AK M HK SGVLRK | SREBP2 |
| KRTAH-NAIE--KRYRSSINDK I VELK-DLVGTEAKLNKSAVLRK | ADD1 |
| R* H NI * **YR*** K*** D** * * S * K | |
| LTALTKKYRITEND-IQIALDDAKINFNEKLS-----QLQTYMIQF | APOB100 |
| AIDYIR-FLQHSNQKLKQENSLR T AV-HKSKSLK--DLVSAC--- | SREBP1 |
| AIDYIK-YLQQVNHKLRQENMWL K LA-NQKNKLLKGIDL G SLV--- | SREBP2 |
| AIDYIR-FLQHSNQKLKQENL T RSA--HKSKSLK--DLVSAC--- | ADD1 |
| * * K Y N* * *K* *N*K *L *** | |

FIG. 10A

Sequence Comparison of DNA-Binding Domains of SREBP 1 (aa 279-452) SEQ ID N0:116, SREBP 2 (aa 287-568) SEQ ID N0:117 and ADD1 (aa 250-421) SEQ ID N0:118 to a Similar Region of Apo B-100 (aa 2024-2234) SEQ ID N0:115.

| | |
|--|---------|
| EFTIVAFVKYDKNQDVHSINLPFFETLQEYFERNRQTIIIVLVLENVQ | APOB100 |
| GPLPTLVSGGTILATVPLVDAEKLPI N RLAAGSKAPASAQSR-GE | SREBP1 |
| QVPTLVGSSGTILTTMPVMMGQEKVP I KQVPGGVKQ-LEPPKE-GE | SREBP2 |
| GPLQTLVSGGTILATVPLVVDTDKLP I HLAAGGKALGSAQSR-GE | ADD1 |
| ***** V * * ***** *Q * ** E * | |
| RKLKHINIDQFVRKYRAAL-GKL P QQANDY L NSFNWERQVSHAKEK | APOB100 |
| KRTAH-NAIE--KRYRSSINDK I IELK-DLVVGTEAKLNKSAVL R K | SREBP1 |
| RRTH-NIIE--KRYRSSINDK I IELK-DLVMGTDAKMHKSGVL R K | SREBP2 |
| KRTAH-NAIE--KRYRSSINDK I VELK-DLVVGTEAKLNKSAVL R K | ADD1 |
| R* H NI * **YR*** K*** D** * * S * K | |
| LTALTKKYRITEND-IQIALDDAKINFNEKLS-----QLQTYMIQF | APOB100 |
| AIDYIR-FLQHSNQKLQENLSLRTAV-HKSKSLK--DLVSAC---- | SREBP1 |
| AIDYIK-YLQQVNHKLRQENMVLKLA-NQKNKLLKGIDLGSLV---- | SREBP2 |
| AIDYIR-FLQHSNQKLQENLTLRSA--HKSKSLK--DLVSAC---- | ADD1 |
| * * K Y N* * *K* *N*K *L *** | |

FIG. 10B

Sequence Comparison of SREBP1 to Apolipoprotein apo A1

apoA1 (1-243) SEQ ID NO: 119 and SREBP1 (aa 233-500) SEQ ID NO:120

DEPPQSPWDRVKDLATVYVDVLKDSGRDYSQFEGSALGKQLNLKLLDNWDSVTSTFSKLREQLGPVTTQEFWDN
QQQVPVLLQP^HF^TKADSLLTAM^KTDGATVK-----AAGLSPLVSG^TTVQTG-PLPTLVSG^G--TILATVPLVVD-

apoA1 SREBP

apoA1
SREBP

LEKETGLRQEMSKDLEEVEKAKVQPYLDDFQKKWQEEMEL YRQKVPEPLRAELQEGARQKLHELQ-EKLSPLGEE
AEKLPINRLAAGSKAPASAQS^RG-----EKRTAHNAIEKRVRSSINDKIIELKDVGTEAKLNKSAVL---
*EK / SK * * * ** *K* -*/ R * * * E* *K ***

MRDRAR--AHVDALRTHLAPYSDELQRLEARLEA-LKEN-----GGARLAEY-HAKATE-----apoA1
-R-KATDYIRF-LQHSNQKLKQENLSRLTAVHKSKSLKDLVSACSGGNTDVLMEGVK-TEVEDTLTPPPSDAGSREBP
R-*A *** * ** --*L R *** -LK*

apoA1
SREBP

HLSTLSEKAKPALEDLRQGLLPVLESKVSFLSALEYTK--
SPFQSSPLSLGSRGGSGDSEDPVF---EDSKAP--EQ-RPSLHSRGM \overline{DR} -SRL-ALCTLV \overline{FLC} -
 $\sqrt{\text{KAP}}$ E* R L * S L AL *

| | apoA1 | SREBP |
|------|-------|-------|
| LNTQ | 1.00 | 1.00 |
| LSCN | 0.99 | 0.99 |
| L | 0.99 | 0.99 |

Sequence Comparison of apoAII (1-77) SEQ ID NO:121 and SREBP1 (aa 353-423)
SEQ ID NO:122

| | |
|--|---------|
| QAKEPCVESLVSQYFQTVTDYGKDLM--- <td>apoA-II</td> | apoA-II |
| EAKLNK--SAVLRKAI---DYIRFLQHSNQKLKQENLSL--RTAVHKSKS-LKDLVSACGSG-GNTD-VLMEGV | SREBP1 |
| *AK\ / S*V --- DY * L - *K*K *L L ****KSK L- L* G* N ***E | |
| GTQPATQ | apoA-II |
| KTEVEDT | SREBP1 |
| -T** \ / | |

FIG. 10D

apoAIV
SREBP1
apoAIV
SREBP1
apoAIV
SREBP1
apoAIV
SREBP1
apoAIV
SREBP1
apoAIV
SREBP1

FIG. 10E

Sequence Comparison of apoAIV (30-376) SEQ ID NO:123 and SREBP1 (aa 330-1146
SEQ ID NO:124

LPELEQQEQEQEQEQVQMLAPLES apoA
LHDCQQ-----MLMRLGGGTTVTSS SREB
L-* *Q ** S

FIG. 10F

Sequence Comparison of acat (fragment 1) SEQ ID NO:125 and SREBP1
(aa 300-486) SEQ ID NO:126

EKMSLRNRLS-KSRENPEEDED-QRNPAKESLETSPNGRIDIKQLIA
EKLPINRLAAGSKAPASASQSRGEKRTAHNAIE-----
EK* * NRL* S* * *-** A***E

acat
SREBP1

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KKIKLTANGRI-DIKQLIAKK-IKLTAEANGRIDIKQLIAKKIKLTAE
KRYRSSINDKIIEIKDLVVGTEAKLNKSYIRFLQHS--NQKLKQENL
K** * **N *I **K*L** *KL - R*/ * R*

acat
SREBP1

AEELKPFFMKEVGSFHDDFVT-----NLI-EKSAS-LDNKAHSF
S--LRTAHVHKSKSLK--DLVSACGSGGNTDVLMEGVKTEVEDKAKPE
* L***K - * D*V* *** E * ***KA*

acat
SREBP1

VRENV-PR-VLNSAKEK
QRPSLHSRGMLD--RSR
-R * -R *L* * *

acat
SREBP1

FIG. 10G

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Sequence Comparison of acat (fragment 2) SEQ ID NO:127 with
SREBP1 (aa 1061-1085) SEQ ID NO:128

| | |
|-----------------------------|--------|
| RRHC-PLKNPTFLDYVRPRSWTCRYVF | acat |
| RRRAGPGGKGGAVAELEPRPTRREH | SREBP1 |
| RR* P ** * PR | |

FIG. 10H

Sequence Comparison of apoE (aa 124-181) SEQ ID NO:129 and SREBP1 (aa 302-360) SEQ ID NO:130

| | |
|---|--------|
| AMLGQSTEE-LRVRLA--SHL-RKLRKRLRDADDLQKRL-AVYQAGAREGAERGLSAIRE-RL | apoE |
| KLPINRLAAGSKAPASQSRGEKRT---AHNA--IEKRYRSSIN--DKIIELKDLVVGTEAKL | SREBP1 |
| ** * ** ** S* ** **** **KR* * ** * \/* L * E *L | |
| --GPLVEQGRVRAATVGSLAGQPLQERAQAWGERLRARMEEMGSRT-RDRLDEVKEQVA | apoE |
| NKSAVL---R-RAIDYIRFLQHSNQIKQENLS-LRTAVHK--SKSLKD-LVSAÇGSGG | SREBP1 |
| *** R KA* * ** Q Q LR* S* *D 1 * * | |

FIG. 10I

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Sequence Comparison of apoC-II (aa 1-42) SEQ ID NO:131 with
SREBP1 (aa 231-275) SEQ ID NO:132

| | |
|---|---------|
| TQQPQQDEMPSTFLIQVK-----ES--LSSWE---- <td>apoC-II</td> | apoC-II |
| SQ-IQQ-----VPVLLQPHFIKADSLLLTAMKTDGATVKAAGLSPLVSGTT | SREBP1 |
| *Q *QQ * *L Q** *S L*** **K*A* ** | |

FIG. 10J

Sequence Comparison of apoC-III (aa 7-51) SEQ ID NO:133 with
SREBP1 (aa 314-360) SEQ ID NO:134

| | |
|--|--------|
| SLLSFMQGYMKHATKTAKDAL--SSVQESQVAQQARGWTDGFSSLK-- | apoC-I |
| APASQSRGEKRTAHNATEKRYRSSIND-KIIE-LKDLVVGTEAKLNKS | SREBP1 |
| ***S K*** A *SS***-*** ** *L | |

FIG. 10K

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Sequence Comparison of APO C-III (aa 52-79) SEQ ID NO:135 with
SREBP1 (aa 717-748) SEQ ID NO:136

| | |
|---|----------|
| DYWT--VKDKFEFWDLPVPR--TSAVAA | apoC-III |
| EIYVAAALRVKTSLSLPRALHFLTRFFLSSARQA | SREBP1 |
| *** * * \bar{x} \bar{K} S * $\bar{-}$ L $\bar{-}$ * \bar{R} * *SA $\bar{-}$ A | |

FIG. 10L

Sequence Comparison of apo D (aa 30-34) SEQ ID NO:137 with SREBP1
(aa 301-305) SEQ ID NO:138

| | |
|-------|--------|
| EKIPT | apoD |
| EKLPI | SREBP1 |
| EK*p | |

FIG. 10M

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Sequence Comparison of apo D (aa 36-65) SEQ ID NO:139 with SREBP1
(aa 361-391) SEQ ID NO:140

| | |
|---------------------------------|--------|
| ENGRCIQANYS-LME-NGKIKVLNQELRADG | apoD |
| AVLRKA-IDYIRFLQHSNQKIKQENLSRTAV | SREBP1 |

FIG. 10N

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Comparison of the Primary Structures of Known Coiled-Coil Regions of
DNA-Binding Proteins and Analogous Regions in Apo B-100

| | | |
|--|-----------------|-----------------|
| <u>M</u> <u>K</u> <u>Q</u> <u>L</u> <u>E</u> <u>D</u> <u>K</u> <u>V</u> <u>E</u> <u>E</u> <u>L</u> <u>L</u> <u>S</u> <u>K</u> <u>N</u> <u>Y</u> <u>H</u> <u>L</u> <u>E</u> <u>N</u> <u>E</u> <u>V</u> <u>A</u> <u>R</u> <u>L</u> <u>K</u> <u>K</u> <u>L</u> <u>V</u> <u>G</u> <u>E</u> <u>R</u> | GCN4-p1 | (SEQ ID NO:141) |
| <u>K</u> <u>H</u> <u>E</u> <u>I</u> <u>Q</u> <u>E</u> <u>M</u> <u>F</u> <u>D</u> <u>Q</u> <u>L</u> <u>R</u> <u>A</u> <u>K</u> <u>E</u> <u>K</u> <u>E</u> <u>L</u> <u>R</u> <u>T</u> <u>W</u> <u>E</u> <u>E</u> <u>E</u> <u>L</u> <u>T</u> <u>R</u> <u>A</u> <u>A</u> <u>L</u> <u>Q</u> <u>Q</u> | hMLK1(286-317) | (SEQ ID NO:142) |
| <u>E</u> <u>E</u> <u>L</u> <u>L</u> <u>R</u> <u>R</u> <u>R</u> <u>E</u> <u>Q</u> <u>E</u> <u>L</u> <u>A</u> <u>E</u> <u>R</u> <u>E</u> <u>I</u> <u>D</u> <u>I</u> <u>L</u> <u>E</u> <u>R</u> <u>E</u> <u>L</u> <u>N</u> <u>I</u> <u>I</u> <u>H</u> <u>Q</u> <u>L</u> <u>C</u> <u>Q</u> | hMLK1(321-352) | (SEQ ID NO:143) |
| <u>R</u> <u>I</u> <u>Q</u> <u>I</u> <u>Q</u> <u>E</u> <u>K</u> <u>L</u> <u>Q</u> <u>Q</u> <u>L</u> <u>K</u> <u>R</u> <u>H</u> <u>I</u> <u>Q</u> <u>N</u> <u>I</u> <u>D</u> <u>I</u> <u>Q</u> <u>H</u> <u>L</u> <u>A</u> <u>G</u> <u>K</u> <u>L</u> <u>K</u> <u>Q</u> <u>H</u> <u>I</u> <u>E</u> | apoB(2232-2264) | (SEQ ID NO:144) |
| <u>V</u> <u>L</u> <u>Q</u> <u>Q</u> <u>V</u> <u>K</u> <u>I</u> <u>K</u> <u>D</u> <u>Y</u> <u>F</u> <u>E</u> <u>K</u> <u>L</u> <u>V</u> <u>G</u> <u>F</u> <u>I</u> <u>D</u> <u>D</u> <u>A</u> <u>V</u> <u>K</u> <u>K</u> <u>L</u> <u>N</u> <u>E</u> <u>L</u> <u>S</u> <u>F</u> <u>K</u> <u>T</u> <u>F</u> <u>I</u> <u>E</u> | apoB(2353-2387) | (SEQ ID NO:145) |
| <u>E</u> <u>L</u> <u>S</u> <u>F</u> <u>K</u> <u>T</u> <u>F</u> <u>I</u> <u>E</u> <u>D</u> <u>V</u> <u>N</u> <u>K</u> <u>F</u> <u>L</u> <u>D</u> <u>M</u> <u>L</u> <u>I</u> <u>K</u> <u>K</u> <u>L</u> <u>S</u> <u>F</u> <u>D</u> <u>Y</u> <u>H</u> <u>Q</u> <u>F</u> <u>V</u> | apoB(2379-2409) | (SEQ ID NO:146) |
| <u>H</u> <u>Q</u> <u>F</u> <u>V</u> <u>D</u> <u>E</u> <u>T</u> <u>N</u> <u>D</u> <u>K</u> <u>I</u> <u>R</u> <u>E</u> <u>V</u> <u>T</u> <u>Q</u> <u>R</u> <u>L</u> <u>N</u> <u>G</u> <u>E</u> <u>I</u> <u>Q</u> <u>A</u> <u>L</u> <u>E</u> <u>L</u> <u>P</u> | apoB(2406-2433) | (SEQ ID NO:147) |
| <u>A</u> <u>A</u> <u>K</u> <u>N</u> <u>L</u> <u>T</u> <u>D</u> <u>F</u> <u>A</u> <u>E</u> <u>Q</u> <u>Y</u> <u>S</u> <u>I</u> <u>Q</u> <u>D</u> <u>W</u> <u>A</u> <u>K</u> <u>R</u> <u>M</u> <u>K</u> <u>A</u> <u>L</u> <u>V</u> <u>E</u> <u>Q</u> <u>G</u> <u>T</u> <u>V</u> | apoB(2530-2560) | (SEQ ID NO:148) |
| <u>S</u> <u>A</u> <u>S</u> <u>L</u> <u>A</u> <u>H</u> <u>M</u> <u>K</u> <u>A</u> <u>K</u> <u>F</u> <u>R</u> <u>E</u> <u>T</u> <u>L</u> <u>E</u> <u>D</u> <u>T</u> <u>R</u> <u>D</u> <u>R</u> <u>M</u> <u>Y</u> <u>D</u> <u>M</u> <u>D</u> <u>I</u> <u>Q</u> <u>Q</u> <u>E</u> <u>L</u> <u>Q</u> <u>R</u> <u>Y</u> <u>L</u> | apoB(2475-2509) | (SEQ ID NO:149) |
| <u>C</u> <u>L</u> <u>N</u> <u>L</u> <u>H</u> <u>K</u> <u>F</u> <u>N</u> <u>E</u> <u>F</u> <u>I</u> <u>Q</u> <u>N</u> <u>E</u> <u>L</u> <u>Q</u> <u>E</u> <u>A</u> <u>S</u> <u>Q</u> <u>E</u> <u>L</u> <u>Q</u> <u>I</u> <u>H</u> <u>Q</u> <u>Y</u> <u>I</u> <u>M</u> <u>A</u> <u>L</u> <u>R</u> <u>E</u> <u>E</u> | apoB(4326-4360) | (SEQ ID NO:150) |
| <u>F</u> <u>L</u> <u>I</u> <u>Y</u> <u>I</u> <u>T</u> <u>E</u> <u>L</u> <u>L</u> <u>K</u> <u>K</u> <u>L</u> <u>Q</u> <u>S</u> <u>T</u> <u>T</u> <u>V</u> <u>M</u> <u>N</u> <u>P</u> <u>Y</u> <u>M</u> <u>K</u> <u>L</u> <u>A</u> <u>P</u> <u>G</u> <u>E</u> <u>L</u> <u>T</u> <u>I</u> <u>I</u> <u>L</u> | apoB(4504-4536) | (SEQ ID NO:151) |

FIG. 11

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Comparison of Known ATP-Binding Loop Motifs to Similar Regions in Apo B-100. The critical amino acid H is indicated by (#)

| A: THE HIGH LOOP | | |
|---------------------------------|------------------|-----------------|
| RLLDHRVPETDMTFRHVGSKLIVAMSSWLQ | apoB(1183-1212) | (SEQ ID NO:152) |
| LNFSKLEIQSQVDSQHVGHSVLTAKGMALF | apoB(2954-2983) | (SEQ ID NO:153) |
| NQNFSAENNENIMEAHVINGEANLDFLNI | apoB(3072-3101) | (SEQ ID NO:154) |
| MVVTRIAPSPT-GDPHVGTAIYIAFNAYAWA | TTETS(1-29) | (SEQ ID NO:155) |
| TTVHTRFPPEPNGYLHIGHAKSICLNFGIA | ECQTS(25-54) | (SEQ ID NO:156) |
| KIKLYCGVDPTAQSLHLGNLVPMLVLLHFYV | YSCMSY1(85-114) | (SEQ ID NO:157) |
| PIALYCGFDPTADSLHLGHLVPLLCLKRGQ | ECOTYRS(33-62) | (SEQ ID NO:158) |
| RVTLYCGFDPTADSLHIGNLAAIILTLRRFQ | BACTYRSA(30-59) | (SEQ ID NO:159) |
| RIGAYVGIDPTAPSLHVGHLPLMPLFWMY | NEUTYRSM(95-124) | (SEQ ID NO:160) |
| PIALYCGFDPTADSLHLGHLVPLLCLKRFQ | SYV ECOLI(31-61) | (SEQ ID NO:161) |
| PLKVKLGADPTAPDIHLGHTVVLNKLRFQ | HEAHI1610(31-60) | (SEQ ID NO:162) |

#

FIG. 12A

Comparison of Known ATP-Binding loop Motifs to Similar Regions in Apo B-100. The critical amino acid K is indicated by (#)

B: THE KMSK LOOP

| | | |
|--|--------------------|------------------|
| VSKGLLIFDASSMGPMQMSASVHLDSSKKQHLFVKEVKIDGQF | apoB(1421-1463) | (SEQ ID NO. 163) |
| TIITTPPLKDFSLWEKTGLKEFLKTTKQSFDSLVAQAQYKKNKH | apoB(3113-3155) | (SEQ ID NO. 164) |
| KNRNNALDFVTKSYNETK----IKFDKYKAEKSQDELPRTFQI | apoB(3183-3221) | (SEQ ID NO. 165) |
| DALQYKLEGTTTL---TR----KRGLKLATALSLSNKFVEGSH | apoB(3348-3390) | (SEQ ID NO. 166) |
| RAFGWEAPREYHMPLLRNPDK-TKISKRSHTSLDWYKAEGL | ttets(221-262) | (SEQ ID NO. 167) |
| DNITIPVHPRQYEFRLNLEY-TVMSKRKLNLLVTDKHVEGWD | ecqts(245-287) | (SEQ ID NO. 168) |
| KNKGL--PFGITVPLLTTATGE-KFGKSAGNAVFIDPSINTAY | YSCMSY1(282-320) | (SEQ ID NO. 169) |
| RLHQNQ-VFGLTVPLITKADG-TKFGKTEGGAVWLDPKKTSKY | ECOTYRS(215-254) | (SEQ ID NO. 170) |
| KTKGEARAFGLTIPLVTKADG-TKFGKTESGTIWLDEKETSYP | BACTYRSA(210-249) | (SEQ ID NO. 171) |
| KTALDE-CVGFTVPLLTDSSG-AKFGKSAGNAIWLDPYQTSVF | NEUTYRSM(303-343) | (SEQ ID NO. 172) |
| RLHQNQ-VFGLTVPLITKADG-TKFGKTEGGAVWLDPKKTSKY | SYE ECOLI(213-253) | (SEQ ID NO. 173) |
| SAGKK-PQVAITLPLLVLGDGEKKMSKSLGNYIGVTEAPSDMF | HEAHI1610(202-243) | (SEQ ID NO. 174) |

#

FIG. 12B

Comparison of Known ATP-Binding loop Motifs to Similar Regions in Apo B-100. The critical amino acid K is indicated by (#)

B: THE KMSK LOOP

| | | |
|--|--------------------|------------------|
| VSKGLLIFDASSMGPMASVHLD SKKKQH L FVKEVKIDGQF | apoB(1421-1463) | (SEQ ID NO. 163) |
| TIITTPPLKDFSLWEKTGLKEFLKTTKQSFDSLVAQYKKNKH | apoB(3113-3155) | (SEQ ID NO. 164) |
| KNRNALDFVTKSYNETK-----IKFDKYKAEKSQDELPRTFQI | apoB(3183-3221) | (SEQ ID NO. 165) |
| DALQYKLEGTTTL---TR-----KRGLKLATALSLSNKFVEGSH | apoB(3348-3390) | (SEQ ID NO. 166) |
| RAFGWEAPREYHMPLLRNPKD-TKISKRKSHTSLDWYKAEGL | ttets(221-262) | (SEQ ID NO. 167) |
| DNITIPVHPRQYEF SRLNLEY-TVMSKRKL NLL VTDKHVEGWD | ecqts(245-287) | (SEQ ID NO. 168) |
| KNKGL--PFGITVPLLTTATGE-KFGKSAGNAVFIDPSINTAY | YSCMSY1(282-320) | (SEQ ID NO. 169) |
| RLHQNQ-VFGLTVPLITKADG-TKFGKTEGGAVWLDPKKTSPY | ECOTYRS(215-254) | (SEQ ID NO. 170) |
| KTKGEARAFGLTIPLVTKADG-TKFGKTESGTIWL DKEKTSPY | BACTYRSA(210-249) | (SEQ ID NO. 171) |
| KTALDE-CVGFTVPLLTDSSG-AKFGKSAGNAIWLDPYQTSVF | NEUTYRSM(303-343) | (SEQ ID NO. 172) |
| RLHQNQ-VFGLTVPLITKADG-TKFGKTEGGAVWLDPKKTSPY | SYE ECOLI(213-253) | (SEQ ID NO. 173) |
| SAGKK-PQVAITLPLL VGLDGEKKMSKSLGNYIGVTEAPSDMF | HEAHI1610(202-243) | (SEQ ID NO. 174) |

#

FIG. 12C

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Examples of Nuclear Localization Signal Sequences in the ApoB-100 Amino Acid Sequence Compared to Known NLS Sequences.

Human apoB-100 sequences with 10 amino acids in the spacer region between the bipartite NLS element

| SEQ ID NO. | Sequence | Source of Sequence |
|------------|--------------------|----------------------------|
| 178 | HKNTSTLSCDGSRLHKF | human apoB-100 (1387-1403) |
| 179 | RKLKHINIDQFVRKYRA | human apoB-100 (2070-2086) |
| 180 | RHIQNIDIQHLAGLKKQH | human apoB-100 (2244-2261) |
| 181 | KKGFYKKKQCRPSKGRK | human IGFBP-3 |
| 182 | KKPLDGEYFTLQIRGRER | human p53 fragment 1 |
| 183 | KRALPNNTSSSPQPKKK | human p53 fragment 2 |
| 184 | KKTNLFSALIKKKKKTA | human Ab1 |
| 185 | RKTLNLSLEEAKKKKKED | human apof fragment 1 |
| 186 | RRELDQSLQVAERL TRK | human apof fragment 2 |

FIG. 13A

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Human apoB-100 sequences with 10 amino acids in the spacer region
between the bipartite NLS element

| SEQ ID NO. | Sequence | Source of Sequence |
|--|--------------------|-----------------------------------|
| 187 | RRSYALVSLSFFRKLRL | human ir fragment 1 |
| 188 | RRYGDEELHLCVSRKHF | human ir fragment 2 |
| 189 | KRVAKRKLIQNRRRR | human thyroid receptor fragment 1 |
| 190 | HRSTNAQGS HWKQRKF | human thyroid receptor fragment 2 |
| 191 | KRPPI SDSEELSAKKRK | human af9 |
| 192 | KKGKKPKTEKEDKV KHI | human irf2 |
| 193 | RKRMNRRIAASKCRK RK | human ap1 |
| IGFBP-3 = interferon growth factor binding protein 3; apof = apolipoprotein f; ir-insulin receptor; af9-activation factor 9; irf-insulin response factor 2; ap1 = activation protein 1 | | |

FIG. 13B

Human apoB-100 sequences with more or less than 10 amino acids in the spacer region between the bipartite NLS element

| SEQ ID NO. | Sequence | Source of Sequence |
|------------|-----------------------|----------------------------|
| 194 | RHIQNIDIQHLAGKLKQH | human apoB-100 (2244-2261) |
| 195 | KKITEVALMGHLSCDTKEERK | human apoB-100 (1072-1094) |
| 196 | KHINIDQFVRKYRA | human apoB-100 (2073-2086) |
| 197 | HRNIQEYLSILTDPDGKGKEK | human apoB-100 (4418-4438) |

FIG. 13C

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Human apoB-100 sequences with more or less than 10 amino acids in the spacer region between an imperfect bipartite NLS element

| SEQ ID NO. | Sequence | Source of Sequence |
|------------|----------------------|-------------------------|
| 198 | KEVYGFNPEGKALLKTK | human APOB100 73-90 |
| 199 | KVLVDHFGYTKDDKHEDM | human APOB100 705-723 |
| 200 | KAGKLKFIIPSPKRPVKL | human APOB100 891-908 |
| 201 | RQVSHAKEKLTALTKKYR | human APOB100 2106-2123 |
| 202 | KYQIRIQIEKLQQLKRH | human APOB100 2228-2245 |
| 203 | KGMALFGEKGAEFTGRHDAH | human APOB100 2978-2997 |
| 204 | KQSFDLSVKAQYKKNKHR | human APOB100 3139-3156 |
| 205 | KLEGTTRLTRKRGLK | human APOB100 3353-3367 |
| 206 | KLDVTTSIGRRQHRLR | human APOB100 3662-3676 |
| 207 | KLDFREIQIYKKLR | human APOB100 3735-3748 |

FIG. 13D

Human apoB-100 sequences with more or less than 10 amino acids in the spacer region between an imperfect bipartite NLS element

| SEQ ID NO. | Sequence | Source of Sequence |
|------------|-----------------------|-------------------------|
| 208 | KSPATDLHLRYQDKK | human APOB100 3952-3968 |
| 209 | KYHWEHTGLTLREVSSKLRR | human APOB100 4060-4079 |
| 210 | KDNVFDGLVRVTQKFHMKVKH | human APOB100 4141-4161 |

FIG. 13E

Alignment of Human 2701-3540 SEQ ID NO:214 with Hamster SEQ ID NO:215 and Mouse SE
ID NO:216 apoB-100 Sequences

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-------------------|-------------------|
| L | N | D | F | Q | P | D | L | H | I | P | E | F | Q | L | P | H | I | S | H | T | I | E | V | P | T | F | G | K | L | Y | S | I | L | K | I | Q | S | P | L | F | T | L | D | A | N | A | D | I | G | N | G | T | S | A | N | E | A | - | Human (2701-2760) |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Hamster (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Mouse (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Human (2761-2820) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Hamster (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Mouse (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Human (2821-2880) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Hamster (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Mouse (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Human (2881-2940) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Hamster (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Mouse (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Human (2941-3000) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Hamster (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Mouse (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Human (3001-3060) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Hamster (frag 1) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Mouse (frag 1) | |

FIG. 14A

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Alignment of Human 2701-3540 SEQ ID NO:214 with Hamster SEQ ID NO:215 and Mouse SE
ID NO:216 apoB-100 Sequences

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-------------------|-------------------|-------------------|
| L | N | D | F | Q | P | D | L | H | I | P | E | F | Q | L | P | H | I | S | H | T | I | E | V | P | T | F | G | K | L | Y | S | I | L | K | I | Q | S | P | L | F | T | D | A | N | A | D | I | G | N | G | T | T | S | A | N | E | A | - | Human (2701-2760) | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Hamster (frag 1) | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | Mouse (frag 1) | | |
| G | I | A | A | S | I | T | A | K | G | E | S | K | L | E | V | L | N | F | D | F | Q | A | N | A | Q | L | S | N | P | K | I | N | P | L | A | L | K | E | S | V | K | F | S | S | K | Y | L | R | T | E | H | G | S | E | M | L | F | F | G | Human (2761-2820) |
| I | V | A | S | I | A | A | T | - | G | E | S | E | I | E | A | L | N | F | D | F | Q | A | Q | A | F | L | E | L | N | P | N | P | L | I | L | K | E | S | M | N | F | S | S | K | H | A | R | M | E | H | E | G | E | I | L | F | S | G | Hamster (frag 1) | |
| I | V | A | S | - | V | T | A | K | G | E | S | Q | F | E | A | L | N | F | D | F | Q | A | Q | A | F | L | E | L | N | P | H | P | P | V | L | K | E | S | M | N | F | S | S | K | H | V | R | M | E | H | E | G | E | I | V | F | D | G | Mouse (frag 1) | |
| N | A | I | E | G | S | N | T | V | A | S | L | H | T | E | K | N | T | L | E | S | N | G | V | I | V | K | I | N | N | Q | L | T | L | D | S | N | T | K | Y | F | H | K | L | N | I | P | K | L | D | F | S | S | Q | A | D | L | R | Human (2821-2880) | | |
| K | F | I | E | G | K | L | D | T | V | A | S | L | Q | T | E | K | N | M | V | E | F | N | G | M | I | V | K | I | N | N | P | I | I | L | D | S | H | T | K | Y | F | H | K | L | S | I | P | R | L | D | F | S | S | K | A | S | F | N | Hamster (frag 1) | |
| K | A | I | E | G | K | S | D | T | V | A | S | L | H | T | E | K | N | E | V | E | F | N | G | M | T | V | K | V | N | Q | L | T | L | D | S | H | T | K | Y | F | H | K | L | S | V | P | R | L | D | F | S | S | K | A | S | L | N | Mouse (frag 1) | | |
| N | E | I | K | T | L | K | A | G | H | I | A | W | T | S | S | G | K | G | S | K | W | K | A | C | P | R | F | S | D | E | G | T | H | E | S | I | S | F | T | I | E | G | P | L | T | S | F | G | L | S | N | K | I | N | S | K | H | Human (2881-2940) | | |
| N | E | I | K | M | L | L | E | A | G | H | V | A | W | T | S | S | G | T | G | S | W | N | A | C | P | N | F | S | D | E | G | T | H | S | S | K | I | S | F | T | V | E | G | P | I | A | F | F | G | L | S | N | N | I | N | G | K | H | Hamster (frag 1) | |
| N | E | I | K | T | L | L | E | A | G | H | V | A | L | T | S | S | G | T | G | S | W | N | A | C | P | N | F | S | D | E | G | I | H | S | S | I | S | F | T | V | D | G | P | I | A | F | V | G | L | S | N | N | I | N | G | K | H | Mouse (frag 1) | | |
| L | R | V | N | Q | N | L | V | Y | E | S | G | S | L | N | F | S | K | L | E | I | Q | S | Q | V | D | S | Q | H | V | G | H | S | V | L | T | A | K | G | M | A | L | F | G | E | G | K | A | E | F | T | G | R | H | D | A | H | L | N | G | Human (2941-3000) |
| L | R | V | I | Q | K | L | A | Y | E | S | G | F | L | N | Y | S | M | L | E | V | E | S | K | V | E | S | O | H | V | G | S | S | I | L | T | G | K | G | T | V | L | L | R | E | A | K | A | E | M | T | G | E | H | N | A | D | L | N | G | Hamster (frag 1) |
| L | R | V | I | Q | K | L | T | Y | E | S | G | F | L | N | Y | S | K | F | E | V | E | S | K | V | E | S | O | H | V | G | S | S | I | L | T | A | N | G | R | A | L | L | K | D | A | K | A | E | M | T | G | E | H | N | A | N | L | N | G | Mouse (frag 1) |
| K | V | I | G | T | L | K | N | S | L | F | F | S | A | Q | P | F | E | I | T | A | S | T | N | N | E | G | N | L | K | V | R | F | P | L | R | L | T | G | K | I | D | F | L | N | N | Y | A | L | F | L | S | P | S | A | Q | Q | A | S | W | Human (3001-3060) |
| K | V | I | G | T | L | K | N | S | L | S | F | S | A | Q | P | F | M | I | T | A | S | T | N | D | N | G | N | L | K | V | S | F | P | L | K | L | T | G | K | I | D | F | L | N | N | Y | A | L | F | L | S | P | H | A | Q | Q | A | S | W | Hamster (frag 1) |
| K | V | I | G | T | L | K | N | S | L | F | F | S | A | Q | P | F | E | I | T | A | S | T | N | N | E | G | N | L | K | V | G | F | P | L | K | L | T | G | K | I | D | F | L | N | N | Y | A | L | F | L | S | P | R | A | Q | Q | A | S | W | Mouse (frag 1) |

FIG. 14B

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Alignment of Human 2701-3540 SEQ ID NO:214 with Hamster SEQ ID NO:215 and Mouse Sequence
ID NO:216 apoB-100 Sequence

| | |
|---|-------------------|
| QVSARFNQKYNQNFSA ²⁷⁰¹ GNNENIMEAHVINGEANLDFLNIP ³⁵⁴⁰ LTIPEMRLPYTIIITPPL | Human (3061-3120) |
| QVSARFNQKYNQNFSA ²⁷⁰¹ INNEH ³⁰⁶¹ IEAHVGMNGDANLDFLTIPLTIPEVKLPYIGLTTPLL | Hamster (frag 1) |
| QASTRFNQKYNQNFSA ²⁷⁰¹ INNEH ³⁰⁶¹ IEASIGMNGDANLDFLNIP ³⁰⁶¹ LTIPEINLPYTEFKTPLL | Mouse (frag 1) |
| KDFSLWEKTGLKEFLKTTKQSF ³¹²¹ DL ³¹⁸⁰ SVKAQYKKNK ³¹²¹ HRHSITNPLAVLCEFI ³¹⁸⁰ SQSIKS ³¹²¹ FDRH | Human (3121-3180) |
| KDFS ³¹²¹ IWEETGLK-----KQSF ³¹²¹ DL ³¹⁸⁰ SVKAQYKKNR ³¹²¹ DRHSIAIPLNGFYEFILNNVDSGIGK | Hamster (frag 1) |
| KDFS ³¹²¹ IWEETGLKKEFLKTTKQSF ³¹²¹ DL ³¹⁸⁰ SVKAQYKKN ³¹²¹ SDKHSIVVPLGMFYEFILNNVNSWDRK | Mouse (frag 1) |
| FEKRN ³¹⁸¹ NALDFVTKSYNETKIKFDKYKAEKSQDELPRTFQIPGYTPVVNVEVSPFTIEM | Human (3181-3240) |
| IGKVR ³¹⁸¹ DSALDYLISSYNEAK ³¹⁸¹ NKFEN-----SLIQPSRTFQKRGYTIPFVNIEVTPFTVET | Hamster (frag 1) |
| FEKVR ³¹⁸¹ NALHFLTTSYNEAKIKVDKYKTENSLNQPSGTFQNHGYTIPVVNIEVSPFAVET | Mouse (frag 1) |
| SAFGYVFPKAVMP ³²⁴¹ SF ³³⁰⁰ SILGSDVRVPSYTLILPSLELPVLHVPRNL-KLSLPHFKELCTIS | Human (3241-3300) |
| LASSHVIPK ³²⁴¹ AINTPSVHILGPNVIVPSYRLVLPSELPLVRVPRNLLKFSLPDFKELRTID | Hamster (frag 1) |
| LASRHVIP ³²⁴¹ TAISTPSVTIPGPNIMVPSYKLVLPPELPLVFHGP ³²⁴¹ GNLFKFFLPDFKGFNTID | Mouse (frag 1) |
| HIFIPAMGNITYDFSFKSSVITLNTNAELFNQSDIVAHLLSSSSVIDALQYKLEG ³³⁰¹ TRL | Human (3301-3360) |
| NIYIPALGNFTYDFSFKSSVITLNTNVGLYNRSDIVAHFLSSSSFVTDALQYKLEG ³³⁰¹ TSRL | Hamster (frag 1) |
| NIYIPAMGNFTYDFSFKSSVITLNTNAGLYNQSDIVAHFLSSSSFVTDALQYKLEG ³³⁰¹ TSRL | Mouse (frag 1) |
| TRKRGLKLATALSLSNKFVEGSHNSTVSLTTKNMEVSVAKTTKAEI--PILRMNFKQELNGN | Human (3361-3420) |
| TRKRGLKLATADSLTNK ³³⁶¹ FKGNHDS ³³⁶¹ TFSLT ³³⁶¹ TKKNMEASV-KTT-ANLHAPILTMNFKQELNGN | Hamster (frag 1) |
| MRKRGLKLATAVSLTNK ³³⁶¹ FKGSHDSTISLT ³³⁶¹ TKKNMEASV-RTT-ANLHAPIFSMNFKQELNGN | Mouse (frag 1) |

FIG. 14C

Alignment of Human 2701-3540 SEQ ID NO:214 with Hamster SEQ ID NO:215 and Mouse SEQ ID NO:216 apoB-100 Sequences

| | |
|---|-------------------|
| TKSKPTVSSSM ^{EFKY} DFNSSMLYSTAKGAVD <u>HKLS</u> LESLSYFSIESSTKGDVKGSVLSR | Human (3421-3480) |
| AKSKPIVSSSI ^{ELN} YDFNSSKLYSTAKGGVD <u>HKFS</u> LESLSYFSIESSTKGNIKGSVLSQ | Hamster (frag 1) |
| TKSKPTVSSSI ^{ELN} YDFNSSKLHSTATGGID <u>HKFS</u> LESLSYFSIESFTKGNIKSSFLSQ | Mouse (frag 1) |
| EYSGTIASEANTYLN ^{SK} STRSSVKLQGTSKIDDIWNLEVKENFAGEATLQRIYSLWEHST | Human (3481-3540) |
| EYSGSVASEANTYLN ^S | Hamster (frag 1) |
| EYSGSVANEANVYLN ^S | Mouse (frag 1) |

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FIG. 14D

Alignment of Human 3481-4536 SEQ ID NO:217 with Rat SEQ ID NO:218 apoB-100 Sequence

| | | | | | | | | | |
|-----------------|-----------|--------|--------|-------|-------|--------|--------|------------|-------------------|
| EYSGTIASEANTYLN | SKSTRSSVK | LQGT | SKIDDI | WNLE | VKEN | FAGEAT | LQRI | YSLWEHST | Human (3481-3540) |
| | NSKGRSSVR | LQGASN | FAGI | WNFE | VGEN | FAGEAT | LRRI | YGTWEHNM | Rat (frag 2) |
| KNHLQLEGLFF | TNGEHT | SKATLE | SPWQ | MSAL | VQVH | ASQP | SSFH | DFDLGQ | Human (3541-3600) |
| INHLQVFSY | FDTKG | QTCRAT | LELSP | WTMST | LLQV | HVSQ | PSPLFD | LHHFDQ | Rat (frag 2) |
| NQKIRWKNEVR | IHSGS | FQSQV | ELSN | DQEK | AHLD | IAGS | LEGHL | RFLKNI | Human (3601-3660) |
| NQKVSWKSEV | QVQV | LQHNA | HFSD | NQDE | EVRL | IAGS | LEG | -----QLWDL | Rat (frag 2) |
| ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | Human |
| ENFFLPAFGKS | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | Rat (frag 2) |
| LKLDVTT | SIGRRQ | HLRV | STAF | VYTK | NPNG | YSF | IPVK | VLADKF | Human (3661-3720) |
| LR-ELLQ | IDGKRQ | YLQAST | SLHY | TKNP | NGYLL | SLP | VQEL | TDRF | Rat (frag 2) |
| TFHVP | FTDLQ | VPSC | KLDF | REIQ | IYKK | LR | TSSF | ALNPL | Human (3721-3780) |
| ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | Rat (frag 2) |
| IPFFE | ITVP | ESQ | TVSR | FTLP | KSVSD | GIAAL | DLNAV | ANKIAD | Human (3781-3840) |
| VPTF | ETI | PEIQ | LT | VSQ | FTLP | KSF | PVGN | TVFD | Rat (frag 2) |
| KFSV | PAGI | VP | SFQAL | TAR | FEVD | SPV | NATWS | ASLKN | Human (3841-3900) |
| EF | SV | PAGI | FIP | FFGEL | TAHV | GMA | SPLYN | VTWST | Rat (frag 2) |

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FIG. 14E

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Alignment of Human 3481-4536 SEQ ID NO:217 with Rat SEQ ID NO:218 apoB-100

Sequences

| | |
|--|-------------------|
| LNLVLGTHKIEDGTLASKTKGTLAHRDFAEYEEEDGKFEGLQEWEGKAHLNLIKSPAFTDLH | Human (3901-3960) |
| LKVVGTHRIENDKFIYKIKGTLQHCDFNVKYNEDGIFEGLDWLEGEAHLDITSPALTDHF | Rat (frag 2) |
| LRYQKDKKGISTSAASPAVGTVGMDMEDDDDFSKWNFYSPQSSPDKKLTIFKTELVRVE | Human (3961-4020) |
| LHYKEDKTSVSASASPAGTVSLDASTDDQSVRLHVYFRPQSPDNKLSIFKMEWRDKE | Rat (frag 2) |
| SDEETQIKVNWEEEEASGLL TSLKDNVPKATGVL YDYVNKYHWEHTGL TLREVSSKLRN | Human (4021-4080) |
| SDGETYIKINWEEEEAFRLDLSLKSNNVPKASEAVDYVKKYHLGH-----ASSELRKS | Rat (frag 2) |
| LQNNAEWVYQGAIRQIDIDVRFQKAASGTIGTYQEWKDKAQNLYQELLTQEQQASFOGL | Human (4081-4140) |
| LQNDAEH----AIRMVDEMNVNAQRVTRDITYQSL-YKKMLAQE-----SQSIPEKL | Rat (frag 2) |
| KDNVFDGLVRVTQKFHMKVKHLIDSLIDFLNFRFPQPGKPGIYTREELCTMFIREVGTV | Human (4141-4200) |
| KKMVLGSLVRITQKYHMAVTVLMDSVIHFLKFNRVQFPGNAGTYTVDELVTIAMRETKKL | Rat (frag 2) |
| LSQVYSKVHNGSEILFSYFQDLVITLPFELRKHKLIDVISMYRELLKDL SKEAQEVFKAI | Human (4201-4260) |
| LSQLF----NGLGHLFSYVQDQV-----EKSRVINDI-----TFKCPFSP | Rat (frag 2) |
| QSLKTTTEVLRNLQDLLQFIFQLIEDNIKQLKEMKFTYLINYIQDEINTIFNDYIPYVFKL | Human (4261-4320) |
| TPCKLKDVLLIFREDLNILSNLGGQDINFITILSDFQSFLERLLDIIEEKIEC-LKNN-- | Rat (frag 2) |
| ----- | Human |
| ESTCVPDHINMFFKTHIPFAFKS----- | Rat (frag 2) |

FIG. 14F

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Alignment of Human 3481-4536 SEQ ID NO:217 with Rat SEQ ID NO:218 apoB-100

Sequences

| | |
|---|-------------------|
| LKENLCLNLHKFNEFIQNELQEASQELQQIHQYIMALREEYFDPSIVGwTVKYVELEEKI | Human (4321-4380) |
| LRENIYSVFSEFNDVQSILQEGSYKLQQVHQYMKAFREEYFDPSVVGwTVKYVEIEEKM | Rat (frag 2) |
| VSLIKNLLVALKDFHSEYIVSASNFTSQLSSQVEQFLHRNIQEYLSILTDPDGKGKEKIA | Human (4381-4440) |
| VDLIKTLLAPLRDFYSEYSVTAAADFASKMSTQVEQFVSRDIREYLSMLADINGKGREKVA | Rat (frag 2) |
| ELSATAQEIIKSQAIAATKKIISDYHQQFRYKLQDFSDQLSDYYEKFIAESKRLIDLSIQN | Human (4441-4500) |
| ELSIVVKERIKSWSTAVAEITSDYLRQLHSKLQDFSDQLSGYYEKFVAESTRLIDLSIQN | Rat (frag 2) |
| YHTFLIYITELLKKLQSTTMN--PYMKLAPGELTIIL | Human (4501-4536) |
| YHMFRLRYIAELLKKLQVATANNVSPYLRFAQGELIITF | Rat (frag 2) |

FIG. 14G

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Alignment of Human 4141-4536 SEQ ID NO:219 with Chicken SEQ ID NO:220 apoB-100 Sequences

| | |
|--|-------------------|
| KDNVFDGLVRVTQKFHMKV <u>KHL</u> IDSLIDFLNFRPQFPQKPGIY <u>TREELCTMFIRE</u> GVTV | Human (4141-4200) |
| IPGLSEKYTG <u>EELY</u> LMTTEKAAKT | Chicken (frag 1) |
| LSQVYSKVHNGSEILFSYFQDLVITLPFELRK <u>HKL</u> IDVISMYRELLKDLSKEAQEVFKAI | Human (4201-4260) |
| ADICLSKLQYFDALIAAISELEVRVPAS <u>ETIL</u> RGRNVLDQIK <u>EML</u> KHLQEKIRQTFVTL | Chicken (frag 1) |
| QSLKTTEVLRLNQDLLQFIFQLIEDNIKQLK <u>EMK</u> FTYLINYIQDEINTIFNDYIPYVFKL | Human (4261-4320) |
| QEADFAGKLNRLKQVVQKTFQKAGNMVRSLSQSKNFEDIKVQM <u>QQL</u> YKDAMASDYAHKLRS | Chicken (frag 1) |
| LKENLCLNLHKFNEFIQNELQ <u>EASQ</u> ELQIHQYIMALREEYFDPSIVGWTVKYEELEEKI | Human (4321-4380) |
| LAENVKKYISQIKNFSQTLQKLS <u>ENL</u> QQLVLYIKALREEYFDPTTLGWSVKYEEVEDKV | Chicken (frag 1) |
| VSLIKNLLVALKDFHSEYIVSASNFTSQLSSQVEQFLHRNIQEYLSILTDPDGKGKEKIA | Human (4381-4440) |
| LGLLK ¹ NLMDTLVIWYNEYAKDLSLVTRLTDQVRELVENYRQEY <u>YDL</u> ITDVEGKGRQKWM | Chicken (frag 1) |
| ELSATAQEIIKSQAIAKKIISDYHQQF <u>RYKLQ</u> DFSQSDYQSDYEFIAESKRLIDLSIQN | Human (4441-4500) |
| ELSSAAQEKIRYWSAVAKRKINEHNRQVKAKLQEYIGQLSDSQEKLINVA <u>KML</u> IDLTV EK | Chicken (frag 1) |
| YHTFLIYITELLKKLQSTTVMPYMKLAPGELTIIL----- | Human (4501-4536) |
| YSTFMKYIFELLRWFEQATADSIKPYIAVREGELRIDVPFDWEYINQM <u>PQKSREAL</u> RNKV | Chicken (frag 1) |
| ----- | Human |
| ELTRALIQGVEQGRKWEEMQAFIDEQLATEQLSFQQIVENIQKRMKT | Chicken (frag 1) |

FIG. 14H

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Alignment of Human 1561-1740 SEQ ID NO:221 with Rabbit SEQ ID NO:222 apoB-100
Sequences

| | |
|--|-------------------|
| DMTFSKQNALLRSEYQADYESLRFFSLLSGSLNSHGLELNADILGTDKINS ^{GAHKATLRI} | Human (1561-1620) |
| DLTFSKQNALLRAEYQADYKSLRFFFTLLSGLLNTHGLELNADILGTDK ^{MNTAAHKATLRI} | Rabbit (frag 1) |
| GQDGI ^{STSATTNL} KCSLLVLENELNAELGLSGASM ^{KLTTNGRFR} EHNAKFSLDGK ^{AALTE} | Human (1621-1680) |
| GQNGV ^{STSATTSLRYSPLMLENELNAELALSGASM} KLATNGR ^{FK} EHNAKFSLDGK ^{ATLTE} | Rabbit (frag 1) |
| LSLGSAYQAMILGVDSKNIFNFKV ^{SQ} EGLKLSNDMMGSYAEMK ^{FDHTNSLNIAGLSLDFS} | Human (1681-1740) |
| LSLGSAYQAMILGADSKNIFNF----- | Rabbit (frag 1) |

FIG. 14I

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Alignment of Human 3301-3720 SEQ ID NO:223 with Rabbit SEQ ID NO:224 apoB-100 Sequences

| | |
|--|-------------------|
| HIFIPAMGNITYDFSKSSVITLNTNAELFNQSDIVAHLLSSSSVIDALQYKLEGTTRL - | Human (3301-3360) |
| MASEKGPSNKDYT | Rabbit (frag 2) |
| TRKRGLKATALSLSNKFVEGSHNSTVSLTTKNMEVSVAKTTKAEIPILRMNFKQELNGN | Human (3361-3420) |
| LRRRI - - - - - EPWEFEVFFDPQELRKEACLLYEIKWGASSKTWRSSGKNTTNH-VEVN | Rabbit (frag 2) |
| - - - - - | Human |
| FLEKLT | Rabbit (frag 2) |
| TKSKPTVSSSMFKYDFNSSMLYSTAKGAVDHLKLSLESLTSYFSIESSTKGDKGVLSLR | Human (3421-3480) |
| - - - - - | Rabbit (frag 2) |
| EYSGTIASEANTYLSKSTRSSVKLQGTSKIDDIWNLEVKENFAGEATLQRIYSLWEHST | Human (3481-3540) |
| RKEACLLYEIKWGASSKTWRSSGK-NTTNHVEVNF-LE-KLTSEGR LGPSTCCSI - - - - - | Rabbit (frag 2) |
| KNHLQLEGLFFFTNGEHTSKATLELSPWQMSALVQVHASQPSFDFPDLGQEVNANTK | Human (3541-3600) |
| TWFLSWS--PCWECSMAIREFLSQHPGVTLIIFVARLFQHMDRRNRQGLKDLVTSGVTVR | Rabbit (frag 2) |
| NQKIRWKNEVR IHGSFQSQVELSNDQEKALHDIAGSLEGHLRFLKNIILPVYDKSLWDF | Human (3601-3660) |
| VMSVSEYCYCWFENFVNPYPGKAAQWPYPYPRWMLMYALELYCIILGLPPC - - - - - | Rabbit (frag 2) |
| LKLDVTTSIGRRQHLRVSTAFVYTKPNPGYSFIPVKVLADKFITPGLKLNLDNSVLVMP | Human (3661-3720) |
| - - - - - LKISRRHQKQL - - - - - TFFSLTPQYCHYKMIIPPYILLATGLLQPSVPWR | Rabbit (frag 2) |

FIG. 14J

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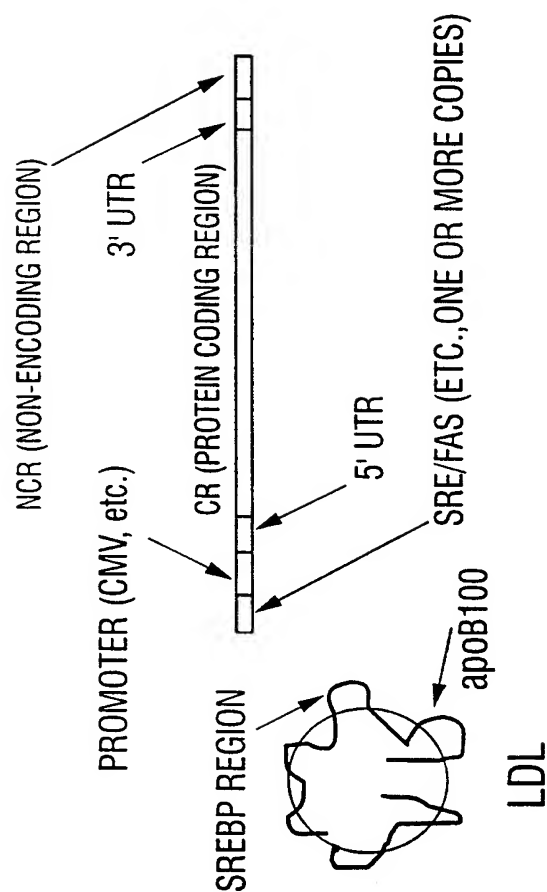


FIG. 15

INTERNATIONAL SEARCH REPORT

Inter- national Application No

PCT/US 98/11927

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/87 C07K14/775 A61K47/48 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-------------------------------------|
| X | KIM J.S. ET AL.: "Terplex system of lipoprotein, cationic polymer and DNA for gene delivery" PHARM. RES., vol. 12, no. 9 suppl., 1995, page S80 XP002079291 see abstract | 1,4,5, 20,40, 44,45, 64-66 |
| A | WO 87 02061 A (BIOTECH RES PARTNERS LTD) 9 April 1987 see abstract see page 1 - page 3 see example 1 | 1-65 |
| A | WO 93 04701 A (UNIV CONNECTICUT) 18 March 1993 see abstract see page 5, line 17 - page 8, line 3 | 1-65 |

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

2 October 1998

Date of mailing of the international search report

13/10/1998

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Authorized officer

Galli, I

INTERNATIONAL SEARCH REPORT

Inter: nal Application No
PCT/US 98/11927

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-------------------------------------|
| A | WO 95 31557 A (CLONEXPRESS INC) 23 November 1995 see abstract see table 1 ---- | 1-65 |
| A | WO 95 28494 A (TARGETED GENETICS CORP ;OVERELL ROBERT W (US); WEISSER KAREN E (US) 26 October 1995 see abstract ---- | 1-65 |
| A | BLACKHART B.D. ET AL.: "An expression system for human apolipoprotein B 100 in a rat hepatoma cell line" J. BIOL. CHEM., vol. 265, no. 15, 25 May 1990, pages 8358-8360, XP002079292 see the whole document ---- | 1-65 |
| A | KANEDA Y ET AL: "INCREASED IEXPRESSION OF DNA COINTRODUCED WITH NULCEAR PROTEIN IN ADULT RAT LIVER" SCIENCE, vol. 243, 20 January 1989, pages 375-378, XP000602256 see the whole document ---- | 1-65 |
| A | GUEVARA J. ET AL.: "Evidence that ApoB100 of LDL is a novel Src-related protein kinase." J. PROT. CHEM., vol. 14, no. 7, 1995, pages 627-631, XP002079293 see abstract ---- | 1-65 |
| P,X | WO 98 00556 A (UNIV UTAH RES FOUND) 8 January 1998 see abstract see figure 1 ----- | 1,4,5, 20,40, 44,45, 64-66 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/11927

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 53 - 63
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/11927

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
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| WO 8702061 | A | 09-04-1987 | AU 6408586 A EP 0238645 A | 24-04-1987 30-09-1987 |
| WO 9304701 | A | 18-03-1993 | AU 681997 B AU 2678092 A CA 2116107 A EP 0666923 A JP 7500820 T | 18-09-1997 05-04-1993 18-03-1993 16-08-1995 26-01-1995 |
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